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## EXPERIMENTAL NOTES ON THE INFLUENCE OF THE ADRENALS OVER THE PANCREAS

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In a series of previous contributions, we have dealt at some length with certain relations between the pancreas and other organs of the body particularly the ductless glands. Our experimental work covered a period of about five years, and it may be well, better to understand our present remarks, to repeat the main conclusions reached. For our present purposes they are as follows

1 The flow of juice from the pancreas, whether excited by secretin injected intravenously by HCl placed in the duodenum, or by normal chyme, may be inhibited by the intravenous injection of extracts of the pituitary or adrenal glands

2 This inhibition may last some time after the body as a whole seems to have recovered from the rise in blood-pressure and is independent of systemic blood-pressure. The exact *modus operandi* is not clear

3 Removal of the adrenal glands from otherwise *normal dogs under circumstances* which allow of observation of the flow of pancreatic juice, induces sooner or later a flow from the pancreas which persists until death, and sometimes lasts for hours

4 This flow has been equalled in duration and activity by only the processes natural or experimental, which depend on activation by duodenal secretin

5 It may occur with a fairly high systemic blood-pressure though it generally occurs when the systemic blood-pressure is low

In process of extending our observations and of attempting a solution of some of the many related problems we came across some phenomena which in a rather striking way tend to corroborate our earlier work and also present some points of interest themselves. We are reporting them now, in brief form because of interruptions which delayed further consecutive work

Having established to our satisfaction that the removal of the adrenals from dogs induces a flow from the pancreas it remained to be seen what the effect might be on such a flow of the agents which influence that caused by secretin

\* Read before the American Society for the Advancement of Clinical Investigation, Atlantic City, New Jersey May 13 1912

\*Manuscript submitted for publication April 19 1912

If the flow from the pancreas is induced by the removal of an influence which the adrenals normally exert over that gland the flow should cease when that influence is restored

We tried to adduce evidence on this latter point by direct examination of the blood for epinephrin by means of the Meltzer-Ehrmann frog-eye test by transfusion of the hind legs of the frog (Trendelenburg) and by the use of the unstriped muscle of the intestine (Cannon) but without satisfaction from any of these methods

This failure we do not mean to limit to the examination of the serum of animals deprived of their adrenals, we have not been able, in many attempts to obtain satisfactory results with any method for the quantitative determination of epinephrin in dogs' serum

The frog-eye test of Ehrmann and Meltzer, the transfusion test of Trendelenburg, the colorimetric methods such as that of Comesatti, the intestinal strip of Cannon all work well when epinephrin is being tested in dilution, in sodium chlorid or in Ringer's solution. But when the serum of the dog is being studied the results of control experiments seem to become irregular and unreliable

#### EXPERIMENTS

We experimented then, with a series of seventeen dogs as follows:

The animals were all fasted for 36 hours prior to operation to avoid complicating results from digestive activities, and after anesthetization with ether, the adrenals were removed through the abdomen and a graduated glass cannula was inserted into the pancreatic duct according to the technique described in our earlier articles<sup>1</sup>

The abdominal wound was then closed, a cannula introduced into the trachea to register respiration, and connection established between the carotid artery and a mercury manometer

The respiration and blood pressure were then respectively registered by ink pens at different levels on a kymographion drum supplied with an "endless" roll of paper

The time was marked in seconds on a base line and the flow of pancreatic juice, when it occurred, by noting its passage past divisions on the pancreatic cannula and by electrically registering the same by interruptions in another base line

After establishing the above there ensued a wait of some hours pending a flow of pancreatic juice after a variable period this took place usually with increasing rapidity until, rarely its registration became difficult

<sup>1</sup> Sweet J. E. and Pemberton, Ralph. Experimental Observations on Secretin with Especial Reference to Diabetes and Malnutrition. *THE ARCHIVES INT MED*, February, 1908

Pemberton, Ralph and Sweet J. E. The Inhibition of Pancreatic Activity by Extracts of Suprarenal and Pituitary Bodies. *THE ARCHIVES INT MED*, July, 1908

Pemberton, Ralph and Sweet J. E. Further Studies on the Influence of the Ductless Glands on the Pancreas. *THE ARCHIVES INT MED*, May, 1910

Sweet J. E., and Pemberton, Ralph. The Induction of Pancreatic Activity by the Removal of the Adrenals. *THE ARCHIVES INT MED*, November and December, 1910

Coincidentally there would exist a lowering of the blood-pressure, which was usually somewhat disturbed by the initial operation, but then returned to a fairly constant level, slightly lower than before operation. From here there would shortly ensue, imperceptibly at first, a steady decline of its height until death. We have discussed this in greater detail elsewhere.<sup>1</sup>

Some period was then selected when the pancreatic flow seemed definitely established and an intravenous injection was given of some commercial form of epinephrin.

Coincident with the initial rise of blood-pressure would appear a marked slowing, and, after a few seconds, an apparent cessation, of the pancreatic flow. With or shortly after the return of the blood-pressure to nearly or quite its former level, the pancreatic flow would again appear, at first slowly and then faster until the former rate became equaled or surpassed.

A repetition of the injection of epinephrin would produce identical results, the flow of pancreatic juice ceasing and returning each time. This could be repeated almost indefinitely and in some of our animals was obtained nine consecutive times, the animal in such case being then deliberately killed.

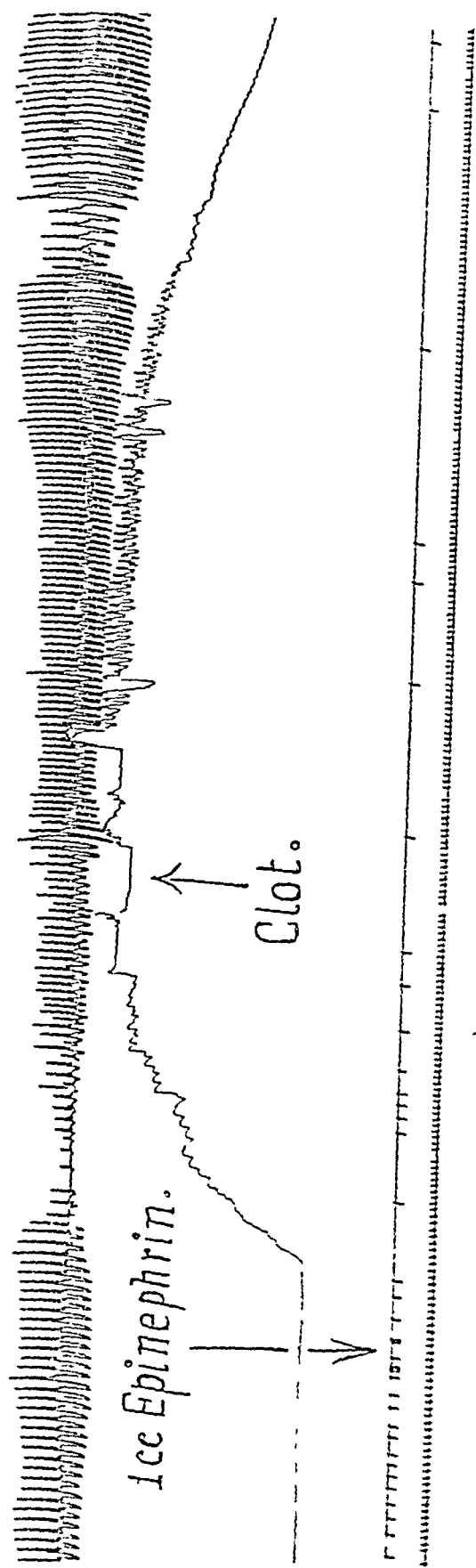
We have in this flow a partial analogue to the condition which sometimes takes place just before death in a normal dog, whose pancreatic flow is similarly watched. In such a dog, there not infrequently occurs what we have elsewhere recorded as a terminal flow, consisting of one or two cannulas (1 to 2 c.c.) of juice. We have previously called attention to the points of similarity between the normal dog after a period of ten to fifteen hours' consecutive etherization, and the dog without adrenals after a period of only three or four hours of anesthesia. The asthenic state, low blood-pressure and tendency to a pancreatic flow in the former are possibly expressions of the same want of suprarenal secretion which possibly exists in the latter.

The entire consonance of the inhibition of pancreatic flow with the injections of adrenalin and rise of blood-pressure on the one hand and the return of the pancreatic flow with a fall of blood-pressure on the other, is strikingly significant. And if it be borne in mind that the pancreatic flow exists apparently only because of the ablation of the adrenals, there seems to be found a strong argument for correlation of action between the two glands.

It does not follow of course that the rise and fall of blood-pressure occurring after the injection of epinephrin are in themselves causative, respectively, of the inhibition and return of pancreatic flow. They tend only to corroborate the belief that the amount of available epinephrin is then diminished or absent, and the action of the injected epinephrin on the pancreas may be by means other than vasoconstrictor, as some of the evidence indicates.

Summing up the situation, then, it seems possible that the flow of pancreatic juice which follows the removal of the adrenals, occurs coincidentally with a diminution or absence of the blood-pressure-raising or other principle of these glands.





Record 1 — (From Experiment 8) The section shown was preceded by four injections and followed by one injection (six in all), giving similar results. It shows the flow produced by removing the adrenals, the inhibition of this flow by 1 c c epinephrin and the return and persistence of the flow when the effect of the epinephrin wears off. (This dog received earlier a transfusion of normal dog's blood, but Record 2 and other Experiments, show that the end result was not thereby affected)

Hand-drawn graph showing the effect of  $\frac{1}{4}$  cc Epinephrin. The graph features a horizontal baseline with a series of small, regular, low-amplitude oscillations. A vertical arrow points to the baseline, labeled  $\frac{1}{4}$  cc Epinephrin. Following the injection, the amplitude of the oscillations increases significantly, reaching a higher, more sustained level.

5.55 PM

From Experiment 14 ) The section shown was preceded and followed by four injections (nine in all) giving similar results. It shows the flow produced by the inhibition of this flow by 25 cc epinephrin and the return and persistence of the flow when the effect of the epinephrin wears off.

It shows the flow product  
It shows the flow product

There seems, furthermore, to exist under these circumstances such a determined and definite flow of pancreatic juice, that repeated injection of epinephrin is not sufficient to stop it permanently

One fact which militates against this as a function of normal physiology, is that the flow sometimes occurs late in the life of the animal and in some experiments the flow seems to usher in the end. In such cases the animals can be kept alive, however, for long periods, during which pancreatic flow tends to occur, by repeated injections of epinephrin, after each of which the blood-pressure, previously at a moribund level, is raised to a height compatible with life

It may be argued that the conditions of such a flow are beyond the pale of normal physiological activity, but it must be borne in mind that the flow begins mildly and often or generally when the animal is apparently in excellent condition. Therefore, while we do not assert that the adrenals thus control the pancreas under the usual conditions of life such a possibility cannot be overlooked much less denied in view of this demonstrable, experimental influence

#### CONCLUSIONS

##### *(On the basis of our previous work)*

Intravenous injections of epinephrin inhibit the flow of pancreatic juice, whether this be caused by hydrochloric acid, normal chyme or secretin

This inhibition may last some time after the blood-pressure has apparently returned to normal, and is independent of the systemic blood-pressure

Removal of the adrenal glands from dogs otherwise normal induces a flow of pancreatic juice which may last for hours

It may occur with a fairly high systemic blood-pressure though it generally occurs when the blood-pressure is low

##### *(On the basis of the work now reported)*

1 Injections of epinephrin made when the flow, following removal of the adrenals is at its height inhibit the flow

2 Shortly after or before the blood-pressure falls to its previous level the pancreatic flow returns. It can thus be repeatedly inhibited and it then repeatedly returns. The tendency to flow seems very strong

3 Since removing the adrenals induces a flow and since injections of epinephrin then inhibit the flow and since the flow returns when the effect of the injection wears off (which last can be repeatedly demonstrated in one animal) it is difficult to escape the thought that there is normally some such relation between these glands

## SYNOPSIS OF EXPERIMENTS

*Experiment 1*—Jan 10, 1911 Both adrenals out, blood-pressure gets low, two hours later 2 cc old epinephrin<sup>2</sup> raises it, better condition, 1.5 cc epinephrin given, 2 cc epinephrin, moribund, no result 12 45 p m no flow

*Experiment 2*—Jan 10, 1911 Adrenals out, no flow, early death, no result

*Experiment 3*—Jan 11, 1911 No 1 Both adrenals out, early death, no evident cause, spleen very large

*Experiment 4*—Jan 11, 1911 No 2 Both adrenals out, no result, early death

*Experiment 5*—Jan 12, 1911 Adrenals out, adrenals not broken or squeezed No flow for a long time at start, flow, 0.5 cc epinephrin gives inhibition, return of flow and blood-pressure Dog gets low with flow (terminal), 1 cc epinephrin raises blood-pressure (which falls fairly soon) Flow inhibits but does not return well again

*Experiment 6*—Jan 28, 1911 Both adrenals out by 9 47, removed easily About 2 15 good flow Later 0.25 cc epinephrin inhibits, blood-pressure falls soon, no return for ten minutes, then good flow 0.166 cc epinephrin inhibits, clot, flow soon returns, 1 cc of 1/1,000,000 inhibits, and clots cannula, no rise in blood-pressure, return of flow and death

*Experiment 7*—Jan 30, 1911 Adrenals out, flow good, 0.1 cc epinephrin inhibits, blood-pressure falls rather slowly and flow returns well, 1 cc epinephrin inhibits and flow returns after a rather slow fall, good flow again inhibited by 0.25 cc epinephrin and dog dies

*Experiment 8*—Feb 1, 1911 Both adrenals out at 10 13, flow at 4 p m, transfusion of dog's blood raises blood-pressure, slightly slows flow, flow returns, transfusion then does not raise blood-pressure much and flow continues, very good flow follows, 0.1 cc epinephrin raises blood pressure moderately Flow continues unabated Blood-pressure falls rather soon, 0.2 cc epinephrin raises blood-pressure more, falls rather soon, flow slowed, returns well, 0.25 cc epinephrin affects blood-pressure same way and slows flow returns, 0.5 cc epinephrin raises blood-pressure well, rather quick fall, distinct inhibition, good return, 1 cc epinephrin keeps blood-pressure up fairly well 3½ minutes, marked inhibition, good return, 1 cc epinephrin, sharp rise, clot, inhibition, good return of flow, 4 cc epinephrin keeps blood-pressure up 10 minutes, strong inhibition, good return, dog being kept alive by epinephrin, now allowed to die, 6 10 p m, intestine and stomach empty

*Experiment 9*—Feb 3, 1911 Both adrenals out Flow not affected by transfusion (One adrenal broke in a m) No definite conclusion to be noted

*Experiment 10*—Feb 7, 1911 Both adrenals out at 10 32 a m Not torn, flow, transfusion of dog's blood, rise in blood pressure, some inhibition, returns, then good flow (Not much blood transfused)

*Experiment 11*—Feb 8, 1911 Adrenals taken out No result

*Experiment 12*—Feb 9, 1911 Both adrenals out, right adrenal torn, flow good, in three hours dog gets low, 1 cc epinephrin revives, blood-pressure falls fast flow soon again, transfusion, slight rise, no apparent inhibition, 0.75 cc epinephrin inhibits, slight return of flow as dog dies after four hours

*Experiment 13*—Feb 14, 1911 Both adrenals out, right adrenal badly torn, slight flow—not recorded Transfusion seems to start slight flow, stops, transfusion seems to start it more actively again Later a flow, 0.166 cc epinephrin inhibits with a very slight rise, flow returns, cannula comes out, 0.5 cc epinephrin gives sharp rise and quick fall Killed

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2 The epinephrin used in these experiments was the adrenalin of Parke, Davis & Co

*Experiment 14*—Feb 17 1911 Both adrenals out at 11 08 a m Neither injured Rather poor flow, inhibition by epinephrin, flow returns, at 5 20 good flow (cannula leaking before), 0 25 cc epinephrin inhibits, moderate slow fall of blood pressure and return of flow *dog low*, 0 25 cc epinephrin inhibits, quicker drop flow returns soon 0 25 cc epinephrin quick fall, inhibition return of flow, 0 25 cc epinephrin, inhibition return of flow, dog dying, 0 25 cc epinephrin inhibition, return of flow 0 25 cc epinephrin, good rise, inhibition, return, 0 25 cc epinephrin, clot inhibition return of flow, 0 75 cc epinephrin, big rise, quick drop, return of flow dog allowed to die, 6 30 p m

*Experiment 15*—March 9, 1911 Adrenals out (right torn) No flow *Secretin* given Flow from it Then later a spontaneous flow which lasts some time and then subsides starts again toward end and gives several cannulas full No epinephrin given

*Experiment 16*—March 10, 1911 Both adrenals out neither torn, blood taken late for frog eye test Flow Medulla inhibits and raises blood pressure Flow returns slightly When dog is moribund 0 5 cc epinephrin and artificial respiration bring back life and also flow later moribund again, 10 cc cortex fails to work, 0 5 cc epinephrin causes return of life and blood pressure which falls quickly (Given twice quickly) no real flow again (The specimens of suprarenal cortex and medulla were supplied by Parke, Davis & Co in the form of powder)

*Experiment 17*—March 9 1911 Fed dog normal pancreatic flow, under ether pancreas congested, lacterels white flow later, hemorrhage into pancreatic duct, irritates experiment Killed

*Experiment 18*—March 11, 1911 No result

2224 Locust Street—301 St Marks Square

# THE ABSORPTION OF FOOD IN TYPHOID FEVER "

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Since von Hosslin and the Russian investigators made their studies on the assimilation of foods in fever twenty to thirty years ago, very little work has been done on the subject. In the meantime, the methods of analysis have been improved and the diet in typhoid has in some clinics been increased so much that patients in the height of their fever are given more food than was formerly given in the second week of convalescence. The question naturally arises as to whether the patients are absorbing the food or are passing it undigested through the intestines.

At the suggestion of Dr. Warren Coleman who has for five years been using a very liberal diet in his service at Bellevue Hospital, I undertook a study of the question in his wards. Six patients with typhoid were studied over periods lasting from five to twenty-one days. They were fed the so-called "high calory diet," which consists of about 1 000 c c milk, 300-400 c c 20 per cent cream, 100-200 gm lactose, two or three eggs, a couple of slices of toast and some butter. This furnishes between two and three thousand calories and one or two thousand calories more can be added in the form of larger amounts of the above or in the form of boiled rice, oatmeal, mashed potato, cream of wheat, apple sauce, custard or ice cream. This diet has been fully described by Shaffer<sup>1</sup> and Coleman,<sup>2</sup> and is the only recorded diet which has succeeded in maintaining the patients in nitrogen and weight equilibrium. Clinical experience has shown that patients do well on this diet and it was no surprise to find that they could absorb the enormous amounts of food almost as well as normal individuals.

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<sup>1</sup>From the department of applied pharmacology and the second medical division of Bellevue Hospital, New York. All analyses were made in the laboratory of the department of physiology. I am indebted to Professor Graham Lusk for the privilege of working in his laboratory and for many valuable suggestions during the course of the work, also to Dr. Coleman and Dr. Dana for permission to use patients, in their wards, and to Mr. Rudolph H. Harries and Mr. John M. Janson for their assistance in making many of the analyses.

<sup>2</sup>Manuscript submitted for publication April 13, 1912.

<sup>1</sup> Shaffer and Coleman. Protein Metabolism in Typhoid Fever. THE ARCHIVES INT. MED., 1909, iv, 538.

<sup>2</sup> Coleman. The High Calory Diet in Typhoid Fever. A Study of One Hundred and Eleven Cases. Am Jour Med Sc., 1912, cxlvi, 77.

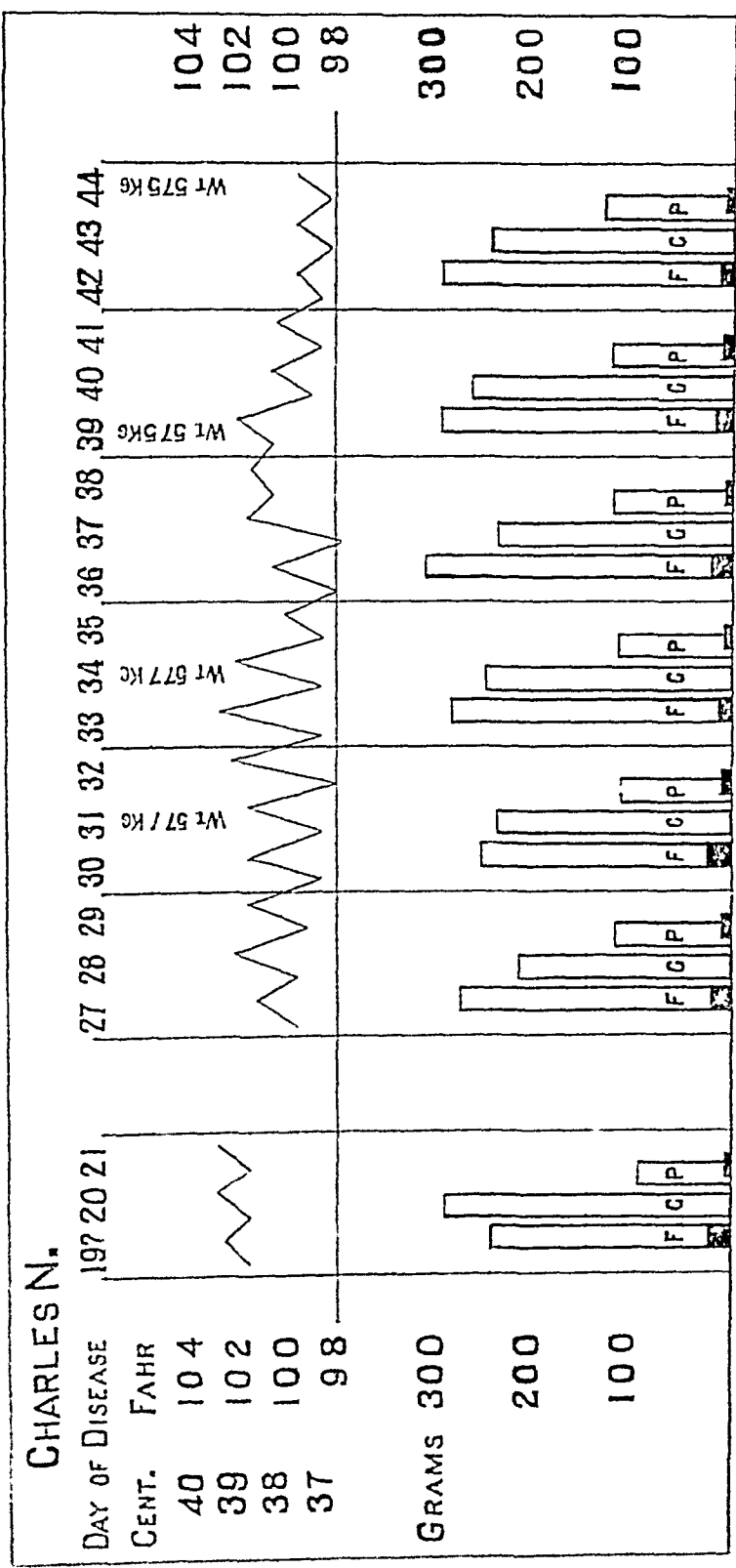


Chart 1—temperature curves in Case I, Charles N. The column shows the average daily weight of fat, carbohydrates and protein in food the solid bases show amounts unabsorbed

## NORMAL ABSORPTION

In the case of normal individuals who are given an easily-digested diet, the food is practically all absorbed and the feces consist almost entirely of bacteria and the secretions of the intestinal tract<sup>3, 4</sup> The feces of a starving person can contain from 0.1 to 0.3 gm of nitrogen a day, and of a person on a nitrogen free diet as much as 0.5 to 0.87 gm of nitrogen. Reducing bodies and ether-soluble substances are also present in the stools when none is given in the food. In addition to these secretions of the intestinal tract, however, considerable amounts of food

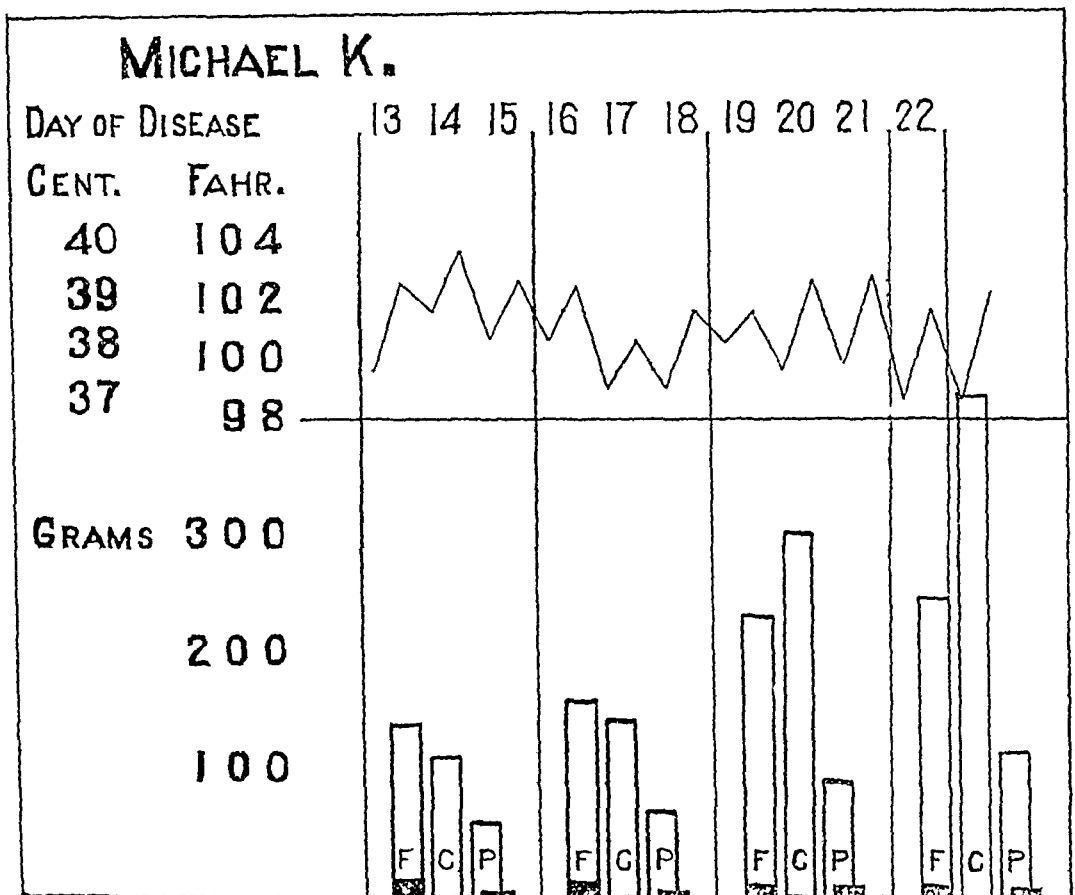


Chart 2—Temperature curves etc, in Case 2, Michael K

residue do appear in normal persons who are given coarse or poorly-cooked food, or food in unusually large quantities. As a rule, sugars are completely absorbed, and well-cooked starches almost completely. Emulsified fats of low-melting point are better absorbed than fats of high-melting point. When fats are given in amounts greater than 350 gm the intestine does not absorb well. (It may be noted that one of the typhoid patients in this series was given 327 gm of fat on one day.) In

<sup>3</sup> Lusk. The Science of Nutrition. Philadelphia 1909, p. 45

<sup>4</sup> Mendel and Fine. Studies in Nutrition, Jour Biol Chem, 1912, vi, 5



considering the absorption of any particular food, such as fat for instance, one can get a false idea if one considers the percentage loss alone without

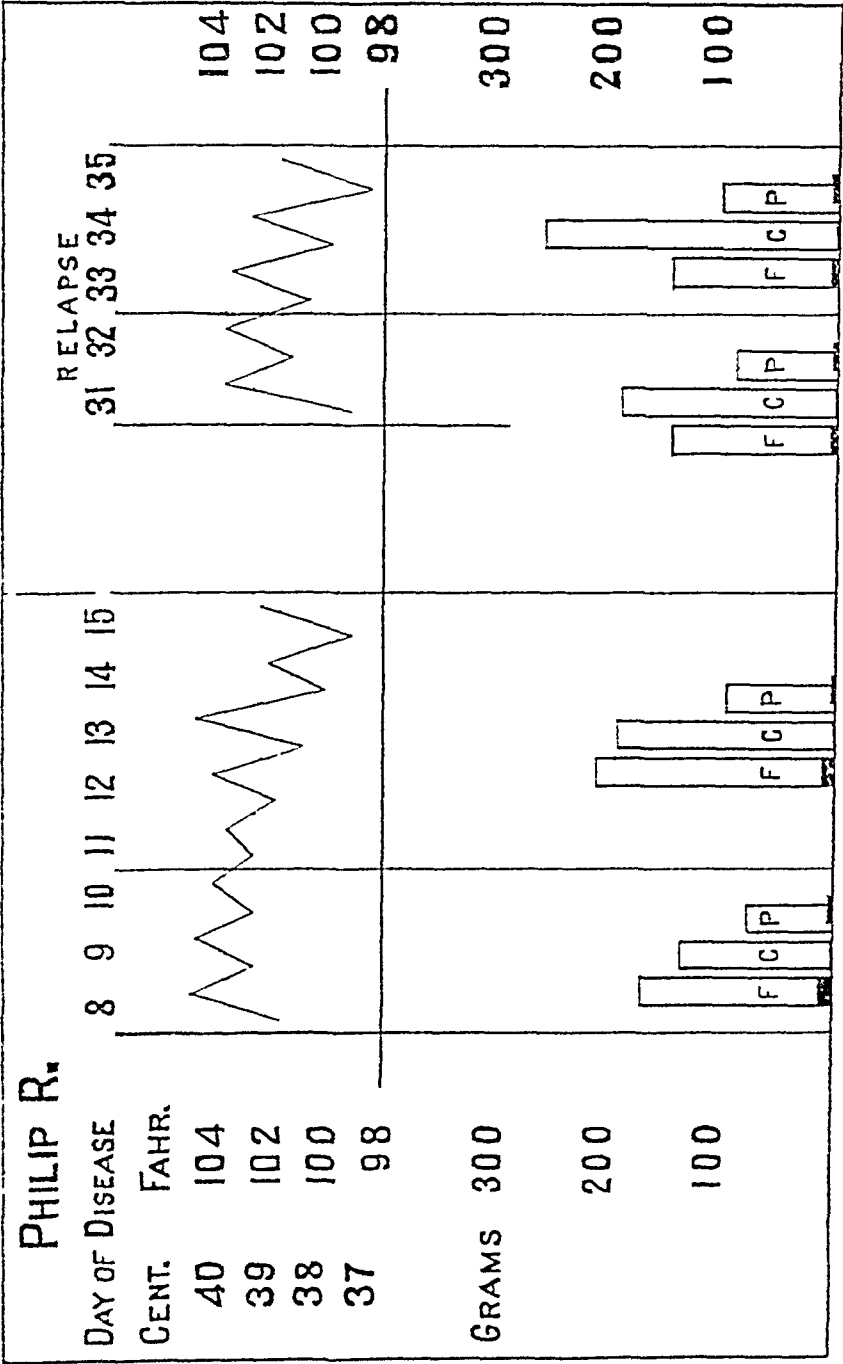


Chart 3.—Temperature Curves etc., in Case 3, Philip R.

considering both the grams of fat in the food and in the feces. This is shown in a series of experiments by von Noorden\* on the same individual

\* Von Noorden. *Lehrb. der Path. des Stoffwechs.* Berlin 1893, p. 17

42 gm fat in food — 57.1 per cent loss in feces  
 42.2 gm fat in food — 10.9 per cent loss in feces  
 80.2 gm fat in food — 6.36 per cent loss in feces

It is hard to state the normal percentage of loss of the various food-stuffs. Rubner<sup>6</sup> gives the accompanying table (Table 1) of the averages of many of his experiments.

TABLE 1—FOOD ABSORPTION, NORMAL INDIVIDUALS

Food	Percentage Loss		
	Fat	Carbo- hydrate	Protein
Roast beef			2.6
Hard boiled eggs	4.4		2.6
Milk	5.2	0	7.1
Fine white bread		1.1	21.8
Rice		0.9	20.4
Potato		0.7	19.5
Mixed diet with			
Bacon (99 gm fat)	17.4	1.6	12.1
Bacon (195 gm fat)	7.8	6.2	14.0
Butter (214 gm fat)	2.7	6.2	11.3
Butter and bacon (350 gm fat)	12.7	6.8	9.2

In certain pathological conditions the absorption of food can be greatly interfered with. Obstruction to the flow of pancreatic juice or bile can diminish the absorption of fats greatly. In certain cases of intestinal indigestion carbohydrates are poorly absorbed. Tuberculosis or cancer of the intestine or any very severe diarrhea can increase greatly the nitrogen content of the feces. A moderate diarrhea has but little effect on absorption.

#### PREVIOUS STUDIES OF ABSORPTION IN TYPHOID

Von Hosslin,<sup>7</sup> in 1882, studied most carefully a series of typhoid patients fed on various diets, such as ham or milk or eggs, or the juice of pressed meat. The total calories of his diets were not high and most of his patients suffered from diarrhea. The nitrogen of the food varied between 10 and 21 gm and the feces nitrogen from 0.9 to 2.2 gm or from 7.6 to 13 per cent of the nitrogen ingested. With 50 to 135 gm of fat in the food the feces contained from 5 to 10 gm or from 6 to 10 per cent. The carbohydrates of the feces were not determined directly. Some of his patients were put on very low diets containing 1 to 3 gm fat, 8 to 11 gm carbohydrate and no protein. During these periods of practical

<sup>6</sup> Rubner, Gruber and Ficker. *Handb. der Hygiene*, Leipzig 1911, 1: 131.

<sup>7</sup> Von Hosslin. *Virchows Arch. f. path. Anat.* 1882, *xxviii*: 95.

starvation, the feces contained 0.8 to 5 gm of ether extract a day and from 0.4 to 0.8 gm of nitrogen. Von Hosslin came to the conclusion that foods were absorbed almost as well in typhoid fever as in health.

Shortly after his work was published the Russians of Chudnowsky's clinic, where typhoid patients were given liberal diets, began a series of investigations on the same subject. Most of their work is published in Russian and has never received the attention it deserves.<sup>8</sup> Their work on the whole supports von Hosslin's contentions. They found the assimilation of protein to be almost as good as in health and they found that cold baths, antipyretics, the drinking of water in large amounts and of alcohol in small amounts seemed to increase the percentage of protein absorbed. Large enemata of hot water seemed to decrease the absorption. Aikinov<sup>8</sup> who included in his dietary 20 gm of blackberries, found from 4 to 6 gm of nitrogen a day in the feces of his patients. Guzdiev,<sup>8</sup> when he gave a very liberal diet of milk and bread with 30 to 45 gm of nitrogen found 4 to 11 gm of nitrogen in the feces. The other observers using moderate and easily-digested diets obtained only 1 to 3 gm per day. Chernoff<sup>8</sup> drawing his conclusions from a small majority of his

<sup>8</sup> Copies of the inaugural dissertations are deposited in the Library of the Surgeon General's Office Army Medical Museum, Washington. Files of Vrach are kept at the Academy of Medicine, New York and probably at most of the other large medical libraries. Abstracts giving some of the tables can be found in Atwater and Langworthy Digest of Metabolism Experiments U. S. Dept of Agri., Bull. No. 45, 1897, p. 181.

It must be remembered that transliterations of the same Russian name may differ greatly.

Chernoff (Tschernoff) Fat Absorption of Adults and Children with and without Fever. Inaug. Diss. (Russian), St. Petersburg, 1883.

Kurkutoff, A. G. (Kurkutow) On the Question of the Influence of Fever and Antipyretic Measures on the Assimilation of Fat by Typhoid Patients. Inaug. Diss. (Russian), St. Petersburg, 1891.

Sassetzky (Zssetszky) Influence of Fever and Antipyretics on the Metabolism and Assimilation of the Proteins of Milk (Typhus fever studied). Inaug. Diss. (Russian), St. Petersburg, 1883. Also Virchow's Arch. f. path. Anat., 1883, xvi, 533.

Khradgi (Chradgi) The Qualitative and Quantitative Assimilation and Metabolism of Nitrogen in Typhoid Fever. Inaug. Diss. (Russian), St. Petersburg, 1886 (abstracted by Puritz). See following paragraph.

Puritz Reichliche Ernährung bei Abdominaltyphus. Virchow's Arch. f. path. Anat. 1893, cxxvi, 327. Also Inaug. diss. (Russian), St. Petersburg.

Matkevich The Influence of Copious Water Drinking on the Assimilation and Metabolism of Nitrogen in Typhoid Fever. Inaug. diss. (Russian), St. Petersburg, 1890.

Guzdiev (Same subject) Vrach, 1890, xi, 213.

Geisler Influence of Enemas on Assimilation and Metabolism of Nitrogen in Typhoid. Vrach, 1890, xi, 479.

Aikinov On Feeding Patients with Alkaline Albuminates of Egg. Inaug. Diss. (Russian), St. Petersburg, 1889.

Dubonov Influence of Alcohol Upon Assimilation and Metabolism of Nitrogen in Typhoid. Inaug. Diss. (Russian), St. Petersburg, 1897.

cases, states that the assimilation of fat is better during the height of typhoid fever than during convalescence or health Kuikutoff,<sup>8</sup> on the other hand, found that the absorption of fat was poorer during fever and varied with the gravity of the disease

On reviewing the figures of all these Russian investigators, one receives the impression that the absorption of food depends chiefly on the patient's general condition and as this is improved either by the natural course of recovery or by therapeutic measures, the absorption of food

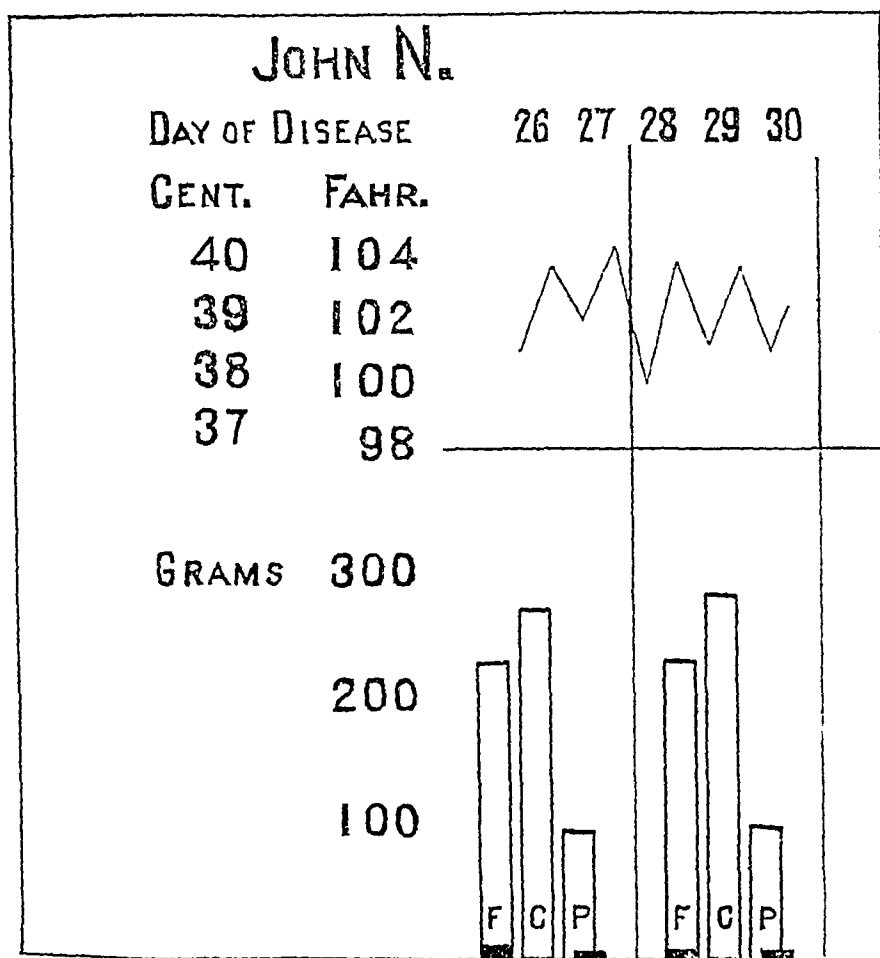


Chart 4—Temperature curves, etc, in Case 4, John N

improves also. It may be noted in passing that the Russians, even when using liberal diets with very large amounts of protein, were unable to keep their fever patients in nitrogen equilibrium.

Von Leyden and Klemperer<sup>9</sup> were the next to study the absorption of foods incidental to their unsuccessful attempt to establish nitrogen equilibrium in typhoid. They found that patients with high fever when given 100 gm of easily-digested fat lost from 6 to 11 per cent in the

<sup>9</sup> Von Leyden and Klemperer. Von Leyden's Handb der Ernahrungstherapie, 1904, II, 332



no case was there any blood in the stools As routine the patients were given no medicine and no tubs, but were sponged for high temperatures

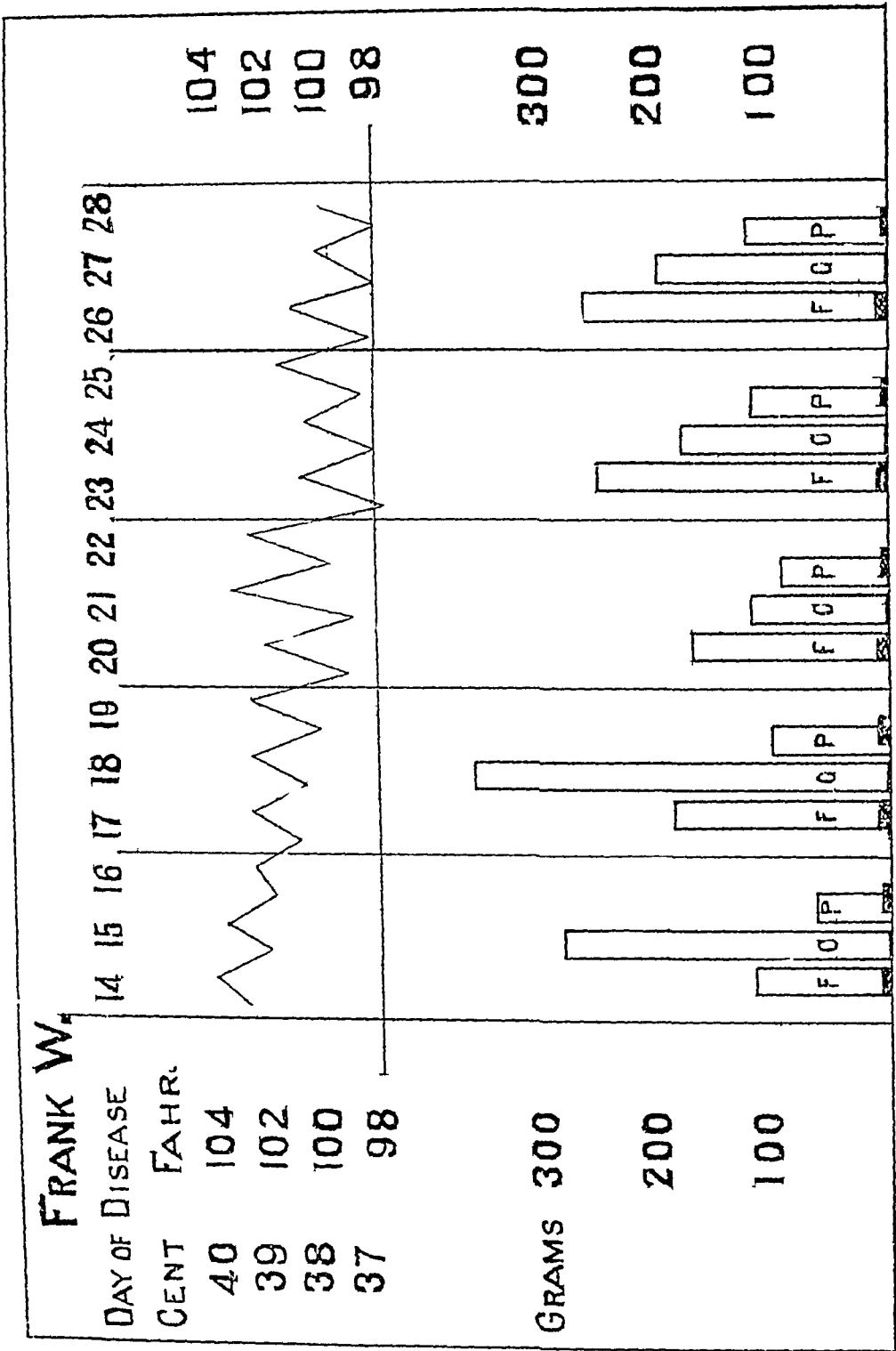


Chart 6 —Temperature curves, etc , in Case 6, Frank W.

Of the cases studied, three, Charles N, Michael K and Frank W. were of rather mild type three Philip R, John N and Charles S, were severe It will be noted that a positive nitrogen balance was obtained in

every case during periods when the temperature was still high. One has difficulty in stating when convalescence begins in such cases. As soon as the temperature starts to show sharp morning remissions the patients look bright and seem comfortable. They read the newspapers, chat with their neighbors, eat their food with relish and rapidly gain weight and nitrogen-containing substances. Relapses are not more frequent on the high diet than on low diets and it is only chance that four of these six patients had relapses. The cases were as follows:

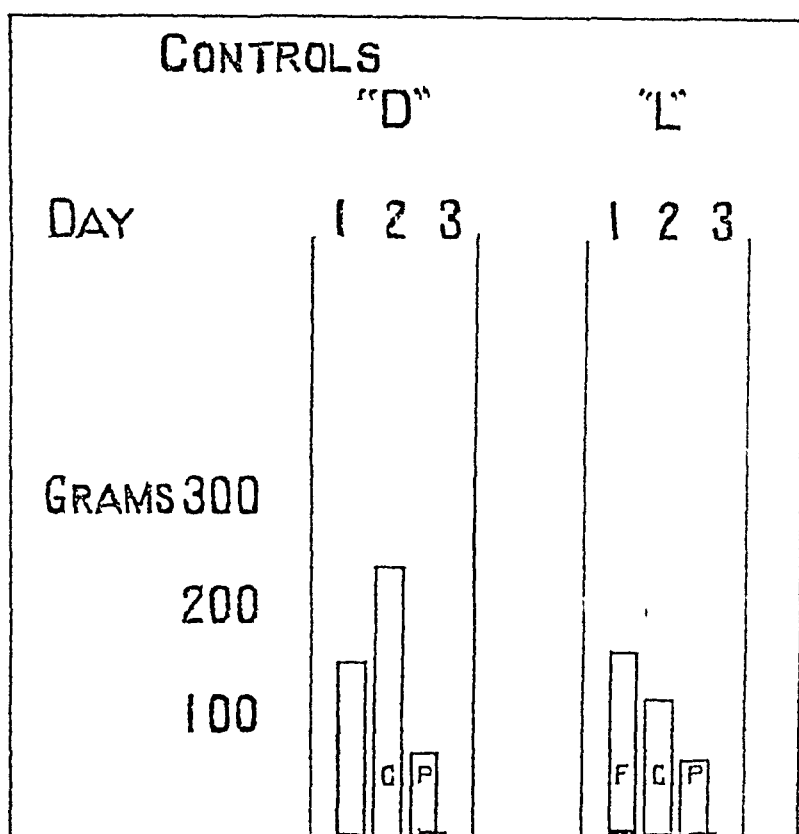


Chart 7—Chart of control Cases "D" and "L"

#### CASE REPORTS

CASE 1—Charles N., 60 years old, admitted Sept. 23, 1910, on the ninth day of the disease.

*History*—The patient has been nursing three typhoid patients in his family. During the last four weeks he has been apathetic and at times dizzy. Date of onset of fever uncertain, probably nine days ago.

*Physical Examination*—Well nourished elderly man. Right eye blind as a result of an old injury. Spleen palpable, several rose spots. Ninth to nineteenth day of disease. Temp 101, 103 F, appetite good, takes 3,000 to 4,000 calories a day, no tympanites, mind clear. Widal test, negative. Nineteenth to twenty-first days, Period I. Twenty-second to twenty-sixth days feces discarded because they were overheated when drying. Twenty-seventh to thirty-fourth days, patient improving steadily. Thirty-fifth day patient has severe pain in the head. Three days later the pain localized in the right eye which became much swollen. Drug

nosis panophthalmitis. On the forty-first day the eyeball ruptured, discharging pus from which the typhoid bacillus was obtained in pure culture. By the forty-fifth day the eye was much improved and two days later the temperature reached normal. The patient made an uninterrupted convalescence.

CASE 2—Michael K., 23 years old, admitted Oct 13, 1910, on eighth day of disease.

*History*—One week before admission the patient began to feel feverish and chilly and suffer from anorexia.

*Physical Examination*—Fairly well nourished young man, apathetic, marked tympanites, rose spots present. Eighth to thirteenth days, temperature 101-104 F. Blood-culture shows typhoid bacilli. Appetite fair, takes 2,000 to 3,000 calories a day. No distention. Thirteenth day, feces collection started. Thirtieth day, temperature normal, convalescence rapid.

TABLE 2—METABOLISM STUDY IN CHARLES N., CASE 1

Day of Disease	Calories			Food, Grams			Urine N + Feces N	Balance	Urine		Body Weight, Kilos
	Total	Per Kg	Carboly- dates (per kg.)	Carboly- dates	Fat	Nitrogen			Vol, cc	Nitrogen	
19 (?)	4600	80	27	383	280	17.0					
20	3200	55	15	209	214	13.5	13.1	+ 0.4	1130	12.0	
27	3910	68	16	226	268	19.2			760		
28	4030	70	17	245	272	19.3	13.2	+ 6.1	1260	11.8	
29	4090	71	14	195	302	19.0	11.5	+ 7.5	890	10.1	
30	3720	64	16	222	253	17.6	11.3	+ 6.3	1060	9.9	
31	4040	70	20	279	261	18.9	15.0	+ 3.9	1520	13.6	57.7
32	4040	70	16	226	261	18.7			1030		
33	4670	81	22	314	311	19.2	12.3	+ 6.9	1290	11.1	
34	3570	62	14	190	251	18.5	12.8	+ 5.7	1520	11.6	57.7
35	4410	76	19	261	305	19.5	14.6	+ 4.9	985	13.4	
36	4300	75	16	223	312	19.8	11.8	+ 8.0	820	10.8	
37	4520	78	19	266	312	20.8	13.3	+ 7.5	1415	12.3	
38	4480	78	17	233	327	18.7	15.3	+ 3.4	1860	14.3	
39	4060	71	16	227	284	19.2	15.2	+ 4.0	1500	13.4	57.5
40	4730	82	24	334	304	20.8	14.6	+ 6.2	1485	12.8	
41	4420	77	18	247	311	20.1	12.0	+ 8.1	1200	10.2	
42	4470	78	18	250	315	20.0	11.9	+ 8.1	1240	10.5	
43	4170	72	18	253	274	22.7			750		
44	4490	78	17	245	314	21.9	10.4	+ 11.5	1100	9.0	57.5

CASE 3—Philip R., aged 23, admitted Oct 19, 1910, on the seventh day of disease.

*History*—For about three weeks the patient has felt chilly and feverish, headache severe, four to five watery stools daily, took to bed six days ago.

*Physical Examination*—Fairly well nourished, pale, torpid, looks toxic, pulse small and weak, many rose spots, temperature 102-105 F.

Eighth to fifteenth days, experimental period. Twelfth day, pulse stronger, a few rales at bases of lungs, abdomen not distended. Thirteenth day, pulse weaker, patient given strychnin, slight distention. Seventeenth to twenty-second days, temperature dropping to normal, patient feels better. Twenty-third to twenty-seventh days, temperature rising in steps to 105 F, pulse weaker. Twenty-seventh to thirtieth days, temperature 102-105 F. Thirty-first to thirty-fifth days, experiment resumed. Thirty-seventh day, temperature normal. Convalescence slow.



TABLE 3—METABOLISM STUDY IN MICHAEL K., CASE 2

Day of Disease	Calories			Food Grams			Urine N + Feces N	Balance	Urine		Body Weight, Kilos
	Total	Per Kg	Carbo hydrates (per kg.)	Carbo hydrates	Fat	Nitrogen			Vol. cc	Nitrogen	
8	1970	35	8	115	134	9.6					
9	1970	35	8	115	134	9.6					
10	2540	45	10	133	176	12.2	13.1	- 0.9	1155	12.2	
11	2540	45	10	133	176	12.2	19.1	- 6.9	845	17.9	
12	2370	42	11	151	154	11.3			Lost		
13	2670	48	13	177	176	12.2	19.8	- 7.6	1940	18.6	
14	3340	60	17	230	215	15.2			Lost		
15	4410	79	27	374	257	19.2	13.4	+ 5.8	1710	11.6	55.9
16	3960	71	25	323	242	14.4	18.2	- 3.8	1820	16.4	
17	4790	86	31	427	257	20.2	17.6	+ 2.6	1200	16.0	

TABLE 4—METABOLISM STUDY IN PHILIP R., CASE 3

Day of Disease	Calories			Food Grams			Urine N + Feces N	Balance	Urine		Body Weight, Kilos
	Total	Per Kg	Carbo hydrates (per kg.)	Carbo hydrates	Fat	Nitrogen			Vol., cc	Nitrogen	
8	2400	44	9	123	166	13.9					
9	2580	48	11	148	179	11.8					
10	2470	45	11	143	175	12.1	16.8	- 4.7	1500	16.1	54.3
11	2830	52	14	186	179	15.8	17.2	- 1.4	1170	16.4	
12	3100	57	13	178	215	15.3	19.7	- 4.4	1200	18.9	
13	2890	53	14	180	191	14.5	20.8	- 6.3	1210	20.0	
14	3460	63	17	230	225	17.2	14.9	+ 2.3	860	14.1	
15	3810	70	16	214	268	17.9	14.9	+ 3.0	1340	14.1	54.7
31	2520	49	14	172	157	15.1	9.7	+ 5.4	900	8.8	51.8
32	2560	50	17	216	144	14.2	13.1	+ 1.1	1300	12.2	
33	2900	56	19	242	160	17.6	13.9	+ 3.7	*	13.1	
34	2880	56	26	310	135	14.1	9.5	+ 4.9	*	5.7	
35	2920	59	20	245	159	18.2	14.0	+ 4.2	*	13.2	49.1

\*Urine volumes made up to 2000 cc

CASE 4—John N., aged 28, admitted Oct. 25, 1910, seventh day of disease. Died December 1.

*History*—Onset six days ago with headache. Since then the patient has had anorexia and diarrhea.

*Physical Examination*—Large frame, fairly well nourished, face flushed, abdomen flat, slight tenderness in left hypochondrium. A few rose spots were found.

Fifth day, blood culture shows typhoid bacilli. Tenth to eleventh days, slight soreness in abdomen and slight distention. Eighth to thirteenth days, temperature 101-101.5 F. Calories of food 2500 to 3500. Fourteenth to twenty-first days, temperature 100-103.6 F. Calories 3000. Twenty-second to twenty-fifth days, temperature 102-105 F. Twenty-sixth to thirtieth days, period of investigation.

tion Thirty first to thirty-fourth days, temperature falling, patient more comfortable Thirty-fifth day temperature shot up to 105 F and a cough developed, during the next few days the left leg developed a boggy edema, the temperature remained high, signs of consolidation appeared in the left upper lobe The patient became very toxic and died on the forty-fourth day of his illness

CASE 5 —Charles S (service of Dr C L Dana), aged 21, admitted Aug 5, 1911, fourth day of disease

History —Onset three days ago with chilly sensations and headache Since then the patient has felt weak and feverish

TABLE 5 —METABOLISM STUDY IN JOHN N, CASE 4

Disease Day of	Calories			Food Grams			Urine N + Feces N	Balance	Urine		Body Weight, Kilos
	Total	Per Kg	Carbohy- drates (per kg)	Carbohy- drates	Fat	Nitrogen			Vol, cc	Nitrogen	
26	3540	55	16	256	227	17 0	11 0	+ 6 0	750	10 0	64 8
27	4030	62	19	301	246	17 4	15 7	+ 1 7	800	14 7	
28	3870	58	18	280	245	18 2	18 0	+ 0 2	1100	17 1	
29	3880	59	22	349	221	16 9	16 4	+ 0 5	850	15 5	
30	3870	58	16	247	246	19 6	18 3	+ 1 3	1000	17 4	

TABLE 6 —METABOLISM STUDY IN CHARLES S, CASE 5

Day of Disease	Calories			Food Grams			Urine N + Feces N	Balance	Urine		Body Weight, Kilos
	Total	Per Kg	Carbohy- drates (per kg)	Carbohy- drates	Fat	Nitrogen			Vol, cc	Nitrogen	
22	2970	51	25	356 6	131 6	11 1	11 4	— 0 3	1255	10 2	58 2
23	4540	78	38	541 8	186 6	16 3	17 5	— 1 2	2350	16 3	
24	5330	92	43	608 1	215 0	19 7	15 7	+ 4 0	1800	14 5	
25	4240	73	33	463 5	205 9	16 8	12 5	+ 4 3	1650	11 3	
26	2820	48	17	243 9	147 2	11 0	23 3	— 12 3	2155	22 1	
27	4450	77	33	465 5	195 0	15 4	14 5	+ 0 9	1110	13 3	58 2
28	4650	80	31	446 2	222 2	16 3	20 1	— 3 8	1220	18 9	

Physical Examination —Well nourished, abdomen flat, spleen palpable, a few rose spots

Fourth to twelfth days, temperature 101-103 F appetite good, not very sick Seventeenth to nineteenth days, temperature normal Twentieth to twenty-third days, temperature rising again in steps Twenty-fourth to thirty-eighth days severe relapse with temperature 102-104 F On the twenty-fifth day a profuse nose bleed occurred followed by several other severe attacks during the next two weeks The patient became very anemic The temperature fell slowly reaching normal on the sixtieth day Convalescence was slow

The respiratory quotients of this patient and of the following case, Frank W, were investigated by Dr Coleman and myself The results will appear shortly

CASE 6—Frank W aged 27 admitted Nov 23 1911 on the tenth day of the disease

*History*—Nine days previously the patient began to have fever headache and pains all over the body

*Physical Examination*—Small frame 5 feet 4 inches tall, well nourished prostrated, apathetic spleen palpable a few rose spots found

Tenth to eleventh days, temperature 103-105 F, appetite poor, diarrhea marked Eleventh to thirteenth days temperature 102 to 105 F, diarrhea has ceased, appetite is improving Fourteenth to twenty-eight days, period of investigation Appetite steadily improving glucose was found in the urine in amounts which increased steadily until he passed 79 gm on the nineteenth day The carbohydrates of the food were then cut down until the sugar disappeared from the urine The temperature fell steadily, reaching normal on the thirty-third day The patient felt strong and was up in a chair when on the forty-seventh day from the onset the temperature began to rise and he went through a moderately severe relapse lasting fifteen days On the seventh day of the relapse bilateral subconjunctival hemorrhages appeared but cleared up in a couple of weeks Repeated urine tests during his rapid convalescence showed no sugar, although he was taking large amounts of carbohydrate

*Controls*—D and L These were two healthy young men between the ages of 25 and 30 They were given the typhoid diet but could not take as large amounts of food as the patients

TABLE 7—METABOLISM STUDY IN FRANK W CASE 6

Day of Disease	Calories			Food Grams			Urine N + Feces N	Balance	Urine				Body Weight, Kilos
	Total	Per Kg	Carbony soup (per kg.)	Carbohydrates	Fat	Nitrogen			Vol, cc	Nitrogen	Glucose	Creatinin	
14	1910	35	21	276.0	67.2	5.9	19.9	-14.0	1222	18.5	Tr	1.67	54.5
15	3380	62	25	333.7	169.2	16.9	16.6	+ 0.3	1210	15.2	7.72	1.28	
16	2510	46	20	267.2	125.1	9.7	15.7	- 6.0	1052	14.3	8.03	1.27	
17	3700	68	26	342.7	198.7	17.4	20.3	- 2.9	1455	18.9	15.48	1.35	
18	3860	71	30	397.3	192.0	17.2	21.3	- 4.1	1675	19.9	31.6	1.59	53.6
19	3690	69	28	373.0	190.3	15.4	19.3	- 3.9	1800	17.9	79.6	1.29	
20	3025	57	13	173.1	202.1	17.0	14.8	+ 2.2	1765	13.8	11.0	.99	
21	2670	50	10	127.7	183.0	17.1	20.9	- 3.8	2050	19.9	8.5	1.17	
22	1860	35	5	65.4	139.3	11.4	13.9	- 2.5	780	12.9	0.0	1.05	52.7
23	2860	54	10	131.4	200.3	17.9	19.7	- 1.8	1545	18.8	0.0	1.11	
24	3980	76	16	201.5	282.4	20.5	17.4	+ 3.1	1575	16.5	0.0		52.5
25	4100	78	17	218.0	288.3	20.6	15.2	+ 5.4	1475	14.3	1.6	1.12	
26	3750	71	15	195.3	264.7	19.0	12.7	+ 6.3	1300	11.9	1.64		53.9
27	3740	71	16	203.4	257.3	20.1	13.1	+ 7.0	1540	12.3	1.8	1.06	
28	4100	76	16	215.0	287.6	21.1	18.2	+ 2.9	1790	17.4	1.6	1.29	

#### METHODS

The patients were under the direct care of the head nurse Miss Mary E Sheehan who has helped in metabolism experiments on typhoid cases for the last three years All food given was measured and recorded Samples of the milk and cream were analyzed from time to time and the other foods were prepared according to known recipes and their food values calculated from the tables of Atwater and Bryant (Bull 28 U S Department of Agriculture)

Every morning the nurse gave an enema of about 250 cc of warm water containing 0.75 gm soap, which amount was, of course, subtracted from the fatty bodies found by analysis in the resulting stool. The results from these enemas were very uniform except in the case of Charles S., in whom an attempt was made to use salt solution instead of the usual soap enema. There was so much retention of feces in the lower bowel for the first three days that soap enemas were again resorted to and the period lengthened to seven days in order to get accurate results.

The periods were marked off at first by a teaspoonful of charcoal, which was somewhat difficult to recognize in the enemas. Later carmin powder in doses of 0.3 gm was used and a most satisfactory line of demarkation obtained. In two of the earlier cases in which the food and stools were very uniform, the demarkation was omitted as the patients objected to the charcoal.

As soon as the initial dose of charcoal or carmin was given, all urine was saved and all the feces as soon as the line of demarkation appeared. The enemas and feces were dried at a temperature below 100° C with the addition of alcohol. The several stools of each period were then united, powdered, passed through a fine sieve and analyzed.

It was feared that the process of drying, which required one or two days, might cause a loss of some of the constituents. To determine this a normal man was put on the high calory typhoid diet and some of the formed stools thoroughly mixed and samples analyzed fresh and after drying in the above manner. The results show that the changes are negligible.

TABLE 8—ANALYSES BEFORE AND AFTER DRYING, EXPRESSED IN PER CENT OF MOIST STOOL IN CONTROL CASE

	Fresh Feces	Dried Feces	Error Caused By Drying
Fat	4.20	4.38	
Average	4.34 4.27	4.43 4.405	+3.2
Carbohydrate	97	92	
Average	97 97	94 93	—4.0
Nitrogen	8.29	8.22	
Average	8.74 8.60 8.543	8.27 8.28 8.257	—3.3

All analyses were made in duplicate and if the results did not agree, were repeated until satisfactory. The nitrogen was determined by the Kjeldahl method, the fats by the complicated but exact method of Kumagawa and Suto,<sup>10</sup> which determines the fats, fatty acids and soaps.

<sup>10</sup> Kumagawa and Suto. Ein neues Verfahren zur quantitativen Bestimmung des Fettes und der unverseifbaren Substanzen in tierischem Material nebst der Kritik einiger gebräuchlichen Methoden. *Biochem. Ztschr.*, 1908, viii, 212. Inaba R. Ueber die Fettbestimmungen des Faeces und einiger Nahrungsmittel nach der neuen Methode von Kumagawa Suto. *Biochem. Ztschr.*, 1908, viii, 348.

together. Results obtained by this method are usually higher than by the older methods of ether extraction which have been shown to be very faulty.

The carbohydrate determinations gave a great deal of trouble. It is impossible to make an accurate sugar test without decolorizing the feces, and many of the methods of decolorization remove sugar as well as color. The dried feces contained from 2 to 4 per cent carbohydrates and after the processes hydrolyzing and decolorizing, the remaining solution for analysis contained about 0.5 per cent dextrose. Accurate sugar determinations with such dilute solutions are difficult.

Various methods of decolorization were tested, using the Allihn method, and the Pavy method as modified by Kumagawa and Suto.<sup>11</sup> 0.25 gm dextrose (Kahlbaum) was added to 4-gm samples of a specimen of dried feces which gave no reduction after boiling with water, although it did reduce after hydrolyzing with 2 per cent HCl. The sample of feces with the added dextrose was boiled five minutes with 80 c.c. distilled water, cooled, 10 c.c. 20 per cent HCl solution added and made up to 100 c.c. Two samples were filtered with difficulty, and Allihn determinations made with the highly colored filtrate. The others were decolorized by the mercuric nitrite method of Patein and Dufau<sup>12</sup> by basic lead acetate, mercuric bichlorid<sup>13</sup> and by acid charcoal.

TABLE 9.—DECOLORIZATION TESTS OF FECES IN CONTROL CASES

Decolorized by	Sugar Method	Per Cent Error in Tests,
Mercuric bichlorid	Allihn	-11, +09
Mercuric bichlorid	Pavy	+9.5, +2.6, -0.2
Mercuric nitrate	Allihn	+3.6, +5.4
Mercuric nitrate	Pavy	-10.5, -5.9
Basic lead acetate	Allihn	-7.2, -5.8
Basic lead acetate	Pavy	-7.9, -15.6
Acid charcoal	Allihn	-10.8, -5.8, +0.8, +5.2, +2.8 Av -1.7
Acid charcoal	Pavy	-11.0, -10.9, -5.1
Filtering, no decolorization	Allihn	-11, +0.9

It was clear that no method gave absolutely satisfactory results but that the error of any method was not great enough to make a significant difference in the findings. When one considers that many carbohydrate determinations in feces are made by the grossly inaccurate method of subtracting the total weight of fat, protein and ash from the weight of

<sup>11</sup> Kumagawa and Suto. Ein Beitrag zur Zuckertitrierung mit ammoniakalischer Kupferlösung nach Pavy. Beitr. z. wissensch. Med. u. Chem. (Salkowski's Festschrift), Berlin, 1904, 211.

<sup>12</sup> Patein and Dufau. Method described in Abderhalden Handb. d. Biochem. Arbeitsmethoden, II, 183.

<sup>13</sup> Ibid., p. 184.

the dried stool, one becomes reconciled to a smaller acknowledged error. The method finally chosen for analysis was the acid charcoal method which seemed more accurate and simpler than any of the others. A specimen of 3 to 4 gm of powdered feces was boiled one and one-half hours in 100 c c 2 per cent HCl, in order to hydrolyze the starches into sugars. After cooling the solution was made up to volume, about 4 gm of the best quality animal charcoal added, filtered, 2 gm more charcoal added, filtered, an aliquot portion rendered slightly alkaline with NaOH to precipitate the phosphates, made up to volume and filtered. With 50 c c of the clear filtrate, Allihn tests were made. In a few cases, the modified Pavy method was used.

Soluble carbohydrates were tested for by boiling a similar sample of feces with water and acidifying after the solution had cooled. Charcoal was then used for decolorization and an Allihn test made. In no case was there more than a very slight reduction. It is an interesting fact that the feces of Michael K, who for his first two periods was given no carbohydrate except lactose, gave 0.4 and 1.2 gm "carbohydrate" after hydrolyzing, but none after plain boiling. Some reducing body or bodies other than carbohydrates must give this misleading result. Possibly mucin caused the reduction.

The indican was tested for in a roughly quantitative manner by Folin's method<sup>14</sup>. One one-hundredth part of the total urine was treated with an equal volume of Obermeyer's reagent and the indigo blue extracted with 5 c c of chloroform and compared with Fehling's solution, which was given arbitrarily the value of 100. The color comparisons were made with Fehling's solution diluted to different percentages and were not made in a colorimeter. This method seems greatly preferable to the old method of recording the result in plus marks. Folin's normal individuals were on a diet very similar to the high calory diet and the indican excretion measured in this method ran between 12 and 140, the average of all six cases being 77.

Glucose in the urine was determined by Benedict's method,<sup>15</sup> which gave most satisfactory results.

#### SUMMARY

Carbohydrates when given in amounts under 300 gm a day were present in the stools only in traces, if, indeed, they were present at all. When amounts larger than 300 gm were given, the stools sometimes contained 2 or 3 gm of reducing bodies.

<sup>14</sup> Folin, Analyses of Thirty "Normal" Urines. *Am Jour Physiol*, 1905, viii, 53.

<sup>15</sup> Benedict, S. R. The Detection and Estimation of Glucose in Urine. *Jour Am Med Assn*, 1911, lxi, 1193.

TABLE 10—COMPARISON OF RESULTS  
CONTROLS

	Fat			Carbohydrate			Nitrogen			Indican in Urine
	Grams in Food	Grams in Feces	Pct cent Loss	Grams in Food	Grams in Feces	Pct cent Loss	Grams in Food	Grams in Feces	Pct cent Loss	
"L"	172	64	38	127	65	05	116	057	50	
"D"	164	31	20	249	25	01	127	100	78	
CHARLES N										
19-21	247	243	98	296	12	04	152	106	70	100
27-29	281	194	68	222	10	04	192	144	75	90
30-32	258	251	97	242	10	04	184	144	78	20
33-35	289	149	52	255	08	03	188	122	65	20
36-38	317	196	61	241	11	04	195	100	51	20
39-41	300	169	56	269	12	04	200	178	89	20
42-44	301	148	49	249	11	04	215	137	64	30
PHILIP R										
8-10	173	145	84	138	04	028	126	068	54	100
11-15	215	117	55	198	04	020	161	078	48	120
31-32	150	65	43	194	04	023	146	086	59	80
33-35	151	63	42	266	06	023	167	092	55	90
MICHAEL K										
13-15	148	166	112	121	04	03	105	092	88	50
16-18	169	162	95	154	12	08	119	120	100	110
19-21	238	117	49	309	24	06	163	179	110	70
22	257	114	44	427	28	06	202	161	80	30
JOHN N										
26-27	236	98	42	278	075	03	172	091	53	105
28-30	237	84	35	292	078	03	182	103	57	90
CHARLES S										
22-28	186.1	15.8	8.5	446.5	1.21	0.27	15.2	1.16	7.6	50
FRANK W										
14-16	120.7	7.9	6.5	292.3	0.93	0.32	10.8	1.40	13.0	15
17-19	193.7	10.8	5.6	371.0	0.58	0.15	16.7	1.42	8.5	60
20-22	174.8	10.2	5.8	122.1	0.51	0.42	15.2	1.01	6.6	25
23-25	257.0	9.0	3.5	183.8	0.53	0.29	19.0	0.88	4.6	25
26-28	269.9	10.0	3.7	204.6	0.74	0.36	20.1	0.84	4.3	25

The nitrogen of the feces averaged 1.12 gm a day, and never exceeded 1.8 gm, amounts which are within normal limits. The percentage loss was 7.1 per cent, which is a figure lower than that of previous observers. This, perhaps, may be due to the fact that the diet was less irritating to the intestinal tract.

With the fats there seems to be a diminution of both the percentage loss and the actual weight of fat in the feces as the disease progresses. It is hard to give averages which are fair, but it can be said that during the first three weeks of the attack and during the height of a relapse, the patients lose on an average 7.2 per cent of the ingested fat. Later in the disease, with a falling temperature and decreasing toxemia, they lose about 4.5 per cent. The average loss for all cases examined was 6.02 per cent, which, though higher than the normal figure of 3 per cent for a similar diet, is not enough higher to be of any clinical significance. The dried feces contained from 30 to 50 per cent fat. It must be remembered that very large amounts of fat were given.

The stools of typhoid fever patients on the high calory diet resemble normal stools very closely. The indican of the urine, which is rather high during the early part of the disease, decreases steadily as the patient's condition improves. The indican excretion compares favorably with that of Folin's normal individuals.<sup>14</sup>

The work of Shaffer and Coleman in establishing nitrogen equilibrium in typhoid fever has been confirmed.

#### CONCLUSIONS

Typhoid patients throughout the disease can absorb carbohydrates and protein as well as normal individuals. They can absorb very large amounts of fat, but the percentage of absorption is somewhat lower than the normal, especially in the earlier part of the disease.

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# THE EFFECT OF A SKIN IRRITANT ON THE LOCAL BLOOD-FLOW IN THE HAND

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It is common knowledge that skin irritants produce reddening of the skin, which may under certain circumstances be followed by the appearance of vesicles, pustules, or a diffuse dermatitis. The effect on the general and the local circulation has been particularly studied in the case of carbon dioxide baths, which differ from most other baths in that they produce a local reddening of the skin. According to O. Miller and his collaborators<sup>1</sup> the reddening of the skin which occurs in these baths is a cutaneous phenomenon and it is not associated with a relaxation of the deeper arteries. Strasburger,<sup>2</sup> who sought to avoid the technical difficulties of working with carbon dioxide baths, added spirits of mustard (*Senfspiritus*) to the water which surrounded the arm in a plethysmograph and he found that when the arm assumed a red color comparable to that seen in the carbon dioxide bath, the arm had increased 4 to 12 c.c. in volume. Yet we doubt if binding conclusions concerning the local blood-flow can be drawn either from changes in arm volume or from variations in the form or size of the pulse, for these do not necessarily indicate the degree of constriction of the finer arterioles, a condition which seems to exercise a predominating influence on the local rate of flow.

It seemed advisable, therefore, to study the effect of skin irritants, using the methods recently described by G. N. Stewart<sup>3</sup> and by Hewlett and Van Zwaluwenburg<sup>4</sup> for determining the rate of blood-flow in the hand and in the arm. Unfortunately neither method is well adapted for studying the local effects of carbon dioxide baths. The evolution of gas excludes the plethysmograph method of Hewlett and Van Zwaluwenburg, and the chemical reaction in the artificial bath would probably interfere with Stewart's calorimetric method. Our experiments have therefore been limited mainly to the effect of baths containing irritating

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\*From the Department of Internal Medicine, University of Michigan.

<sup>1</sup>Manuscript submitted for publication June 19, 1912.

1. Muller, O., and Veiel, E. Beiträge zur Kreislaufphysiologie des Menschen, besonders zur Lehre von der Blutverteilung. Samml. klin. Vortr., 1911, in Med. 194, 195, 196, 199, 200, 201. (Literature.)

2. Strasburger, J. Einführung in die Hydrotherapie und Thermotherapie, 1909, Jena, 243.

3. Stewart, G. N. Studies on the Circulation in Man. Heart, 1911, in 33.

4. Hewlett, A. W., and Van Zwaluwenburg, J. G. The Rate of Blood Flow in the Arm. Heart, 1909, 1, 87.

quantities of mustard, though a few experiments with salt mixtures such as are used in certain Neuheim baths were also performed. In order to ascertain the effect of the irritants, determinations were made simultaneously on the two hands while one was exposed to water containing the irritant and the other to ordinary tap water. In this manner it was possible to eliminate the variations in flow which occur in a single individual at different times. Scrupulous care was taken to maintain the two water baths at the same temperature in order to exclude the effect of local variations in temperature.<sup>5</sup> The results of our experiments are shown in the accompanying tables.

TABLE 1—EFFECT OF MUSTARD BATH ON LOCAL BLOOD-FLOW IN THE ARM  
(Plethysmographic Method)

Subject	Room Temp C	Water Temp C	Average Rate of Flow		Remarks
			Mustard	Control	
Weis	24	34	9.2 <sup>a</sup>	6.2	Arm exposed to mustard felt very warm
Weis	23	33	6.7	2.2	Arm exposed to mustard felt very warm and later smarted considerably. It became swollen the following night and subsequently the skin desquamated.
Wood	22	32.5	3.0	4.2	Arm exposed to mustard felt warm
Wood	18	33	2.9	3.5	Arm exposed to mustard felt warm with slight smarting

\*These figures represent averages of five or more determinations.

TABLE 2—EFFECT OF MUSTARD BATH ON LOCAL BLOOD FLOW IN THE HAND  
(Calorimetric Method)

Subject	Room Temp C	Water Temp C	Average Rate of Flow		Remarks
			Mustard	Control	
Wood	17.5	31	8.3	8.4	
Wood	20.5	30	6.0	5.3	
Weis	18.5	31	4.8	6.8	
Weis	20	30	3.3	4.5	
Weis	20.5	30	3.2	5.9	
Weis	21.5	30.5	8.5	7.6	
Weis	25.5	31.5	9.7	10.6	Hand exposed to mustard smarted but was not reddened.
Weis	27	30.5	4.5	7.0	Hand exposed to mustard was reddened and smarted.
Weis	28	31.8	14.0	13.0	Hand reddened and burned and showed slight dermatitis six hours later.
Weis	28.4	30.5	8.5	11.9	Hand is mustard reddened and smarted.
Weis	30.2	31.4	18	17.4	Hand slightly reddened and smarted.
Weis	30.5	32	14.4	16.9	Hand smarted and was considerably reddened.
Kinde	13.0	29.5	3.1	3.4	
Kinde	14.5	30.5	13.1	11.9	Hand smarted and reddened.
Kinde	15	29.3	8.2	9.0	
Kinde	15.5	30.0	5.0	4.2	
Kinde	18	29	5.5	6.7	
Kinde	19	30.5	6.3	7.4	Hand reddened.
Kinde	19.5	29.5	8.8	7.7	
Kinde	20.5	29.5	6.2	6.3	
Kinde	21	29.8	6.1	5.3	Hand reddened.
Kinde	23	30.0	17.0	10.5	

<sup>5</sup> Hewlett, A. W., Van Zwaluwenburg, J. G., and Marshall, M. The Effect of Some Hydrotherapeutic Procedures on the Blood-Flow in the Arm. *THE ARCHIVES OF INT. MED.*, 1911, vol. 59, 1.

A typical protocol of this group of experiments follows

#### CALORIMETRIC DETERMINATION OF THE RATE OF BLOOD FLOW IN THE HAND

(Weisman—subject, Wood—operator) April 23, 1912

Thermometer (L) in right calorimeter

Thermometer (S) in left calorimeter

Mustard water in right calorimeter

Tap water in the left calorimeter

The right hand was soaked in mustard water at 30 C for seventeen minutes and the left hand in tap water at the same temperature for the same length of time, immediately preceding the experiment. The right hand smarted but was not reddened. Room temperature, 25.5 C

#### PRELIMINARY READING IN CALORIMETERS TO DETERMINE RATE OF HEAT LOSS

Right Calorimeter		Left Calorimeter	
Time	Readings	Time	Readings
1 15	1 540	1 15	3 220
1 16	1 560	1 16	3 240
1 17	1 590	1 17	3 260
1 18	1 620	1 18	3 285
1 19	1 660	1 19	3 310
1 20	1 690	1 20	3 330

Temperature of water in each, 30 C

#### READINGS AFTER INSERTION OF THE HANDS IN CALORIMETER

Right Calorimeter		Left Calorimeter	
Time	Readings	Time	Readings
1 24	1 360	1 24	2 970
1 25	1 270	1 25	2 860
1 26	1 118	1 26	2 740
1 27	1 100	1 27	2 630
1 28	1 030	1 28	2 530
1 29	0 950	1 29	2 430
1 30	0 890	1 30	2 360
1 31	0 810	1 31	2 260
1 32	0 740	1 32	2 160
1 33	0 650	1 33	2 070
1 34	0 590	1 34	2 015
1 35	0 535	1 35	1 950
Temp 31.5 C		Temp 31.5 C	

#### HEAT LOSSES FROM CALORIMETERS AFTER THE HANDS HAD BEEN TAKEN OUT

Right Calorimeter		Left Calorimeter	
Time	Readings	Time	Readings
1 40	0 570	1 40	1 930
1 41	0 600	1 41	1 955
1 42	0 640	1 42	1 980
1 43	0 665	1 43	2 015
1 44	0 700	1 44	2 045
1 45	0 720	1 45	2 080

Weight of mustard solution 1615 gm

Weight of water 1639 gm

Weight of right calorimeter 470 gm

Weight of left calorimeter 470 gm

Volume of the hand substance 485 c c (right)

Volume of the hand substance 510 c c (left)

In the experiments with mustard, the specific heat of the mustard solution was regarded as equivalent to that of an equal weight of water

In the experiments in which the salt solution was used, however, the specific heat was determined by multiplying the actual weight of the solution in grams by 93. Similarly in the following calculations, the actual weights of the calorimeter and of the hand substance were reduced to their water equivalents.

#### CALCULATION OF THE RATE OF BLOOD-FLOW IN THE RIGHT HAND

Calorimeter correction for heat loss in ten minutes	30
With hands in calorimeter for ten minutes the temperature rose to	735

Total rise	1 035
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Water equivalent of the mustard solution	1615
Water equivalent of hand substance	388
Water equivalent of calorimeter	52

Total water equivalent	2055
------------------------	------

Total calories given off from hand in ten minutes	2055 × 1 035 = 2126 9
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Total calories given off from hand in one minute	212 69
--	--------

$$Q = \frac{H}{T - T^1} \times \frac{1}{S}$$

Where Q equals the quantity of blood in grams flowing through the hand in the time of the experiment, H = the heat given off by the hand, T = the temperature of the arterial blood, T<sup>1</sup> = the temperature of the water, S = the specific heat of the blood.

$$Q = \frac{212\ 69}{36\ 5 - 31\ 5} \times \frac{10}{9} = 47$$

Rate of blood flow per minute per 485 c c hand substance = 47

Rate of blood-flow per minute per 100 c c hand substance = 9 7

#### CALCULATION OF THE RATE OF BLOOD-FLOW IN THE LEFT HAND

Calorimeter correction for heat loss in ten minutes	26
With hands in calorimeter for ten minutes temperature rose	909

Total rise	1 169
------------	-------

Water equivalent of water	1639
Water equivalent of hand substance	408
Water equivalent of calorimeter	52

Total water equivalent	2099
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Total calories given off from hand in ten minutes	2099 × 1 169 = 2453 731
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Total calories given off from hand in one minute	245 373
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$$Q = \frac{245\ 373}{36\ 5 - 31\ 5} \times \frac{10}{9} = 54\ 5$$

Rate of blood-flow per minute per 510 c c hand substance	54 5
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Rate of blood-flow per 100 c c hand substance (per minute)	10 6
--	------

Rate of blood-flow in mustard solution	9 7
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Rate of blood-flow in water	10 6
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Difference	9
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TABLE 3—EFFECT OF SALT BATHS\* ON THE LOCAL BLOOD-FLOW IN THE HAND

Subject	Room Temp C	Water Temp C	Average Rate Flow Salt	Control
Kinde	20	28 5	6 4	7 0
Kinde	20 5	29 8	9 7	7 0
Kinde	21	30 5	9 3	9 7
Kinde	21	30 5	9 2	7 8

\*The salt bath contains Na Cl (5 per cent), Ca Cl<sub>2</sub> (5 per cent)

These experiments indicate the considerable variations in the blood-flow of the hand or arm which may occur in a single individual at different times. Such variations are due in part to the temperature of the room<sup>6</sup> and in Table 2 in which the results for each individual are arranged according to room temperatures it will be seen that there is a very definite tendency for the rate to increase on days when the experiments were conducted in a warm room even though the hands were always exposed to water of about the same temperature. It is also evident, however, that other factors than room temperature must have been active to account for the variations from the rule that the rates increase with higher room temperatures. Exactly what these other factors are we have not determined.

So far as we have been able to determine, no definite effect on the local blood-flow results from irritation of the skin by mustard or the salt mixture used. Only in the second experiment of Table 1 was a very marked result obtained and this was associated with a rather severe burn from the mustard which left a dermatitis that did not heal for days. Some doubt is thrown on this experiment by the unusually slow rate in the control arm. Aside from this case the faster of the two hand rates seldom exceed the slower by more than 50 per cent and the difference was about as often in one direction as in the other. It must be admitted that our results throughout are less concordant for the two hands than are those published by Stewart and it is possible that with better technic we should be able to demonstrate some constant difference between the hand exposed to the irritant and the one not so exposed. We feel safe in asserting, however, that the effect if present is but slightly relative to the very marked variations in the blood-flow produced by thermic and by other influence. Certainly it could not be objected that our failure to obtain more marked results was due to insufficient irritation of the skin. In the earlier experiments the hand was exposed to the mustard bath only during its stay of about fifteen minutes in the calorimeter, but in the latter experiments a preliminary soaking in a mustard bath for fifteen minutes or more usually produced redness and smarting before the determination itself was made and these were increased during the determination. We always attempted to stop short of producing a definite dermatitis, but in two experiments at least (No. 2 of Table 1, and No. 9 of Table 2) this occurred. The former has already been alluded to, the latter was not associated with a definitely increased blood-flow during the bath.

Two explanations might be offered for the fact that a local reddening of the skin is not associated with an increased rate of flow in the hand

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<sup>6</sup> Hewlett A. W. The Effect of Room Temperatures Upon the Blood Flow, Etc., *Heart*, III, 1911, 230

In the first place it is possible that although the flow through the skin is increased the flow in the deeper structures of the hand is proportionately diminished so that the resultant of the two is *nil* or nearly *nil*. In the second place the reddening may be due to a dilatation of the small cutaneous capillaries and veins, while the arterioles which are believed to exercise a predominating influence on the local flow are unaffected. We incline toward the latter explanation chiefly for the reason that when the flow in both hands was slow the hand exposed to mustard frequently showed a slightly cyanotic color, which would indicate that the cutaneous vessels were dilated, but that the flow through them was not sufficiently fast to bring much arterial blood to the surface.

#### CONCLUSIONS

1 Irritation of the skin by a mustard bath short of producing a definite dermatitis does not materially increase the rate of blood-flow through the hand relative to the hand whose skin is not so irritated.

2 The local redness is probably due to a dilatation of the cutaneous capillaries and venules without a corresponding dilatation of the underlying arterioles.

# CONCERNING THE PRESENCE IN URINE OF CERTAIN PRESSOR BASES

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Probably the first work on the presence of toxic alkaloid-like bases in putrid meat and urine, and their significance for purposes of diagnosis in disease, was done by Selmi in 1880. In 1884 Bouchard began his development of the idea of urinary toxicity as measured by biological experimentation, and its application to clinical problems. Bouchard's work and that of other French writers, gave an impetus to the investigation of the chemical character of the toxic elements in urine, and in this connection, attention became directed particularly toward those of a basic alkaloid-like nature, and many such have been identified.<sup>1</sup>

In 1906 Abelous<sup>2</sup> directed attention to a certain phase of this subject by isolating from putrid meat a substance, basic in nature, which, when injected into animals, produced a pronounced rise in blood-pressure. He was unable to identify this base with any degree of accuracy, but assigned to it the provisional formula  $C_6H_{11}NO_2$ . Rosenheim<sup>3</sup> in 1909, found that from the products of the putrefaction of fresh human placentas he could isolate two pressor principles which were identical, both physiologically and in melting-point and crystallization, to two substances isolated about the same time by Barger and Walpole from putrid meat, by a somewhat different process than that used by Abelous. However, Barger and Walpole,<sup>4</sup> by using large quantities of meat, were able to obtain these pressor bases in sufficient amount to identify them as isoamylamine and parahydroxyphenylethylamine, which made it probable that they were formed by bacterial decomposition from leucin and tyrosin, respectively, by the splitting off of  $CO_2$ . In 1908 Abelous reported that he had isolated from normal urine a basic substance, soluble in ether, which physiologically was apparently identical with the base he obtained from putrid meat.<sup>5</sup> In 1909 Bain<sup>6</sup> reported having obtained from normal urine, two pressor

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<sup>1</sup>Manuscript submitted for publication June 17 1912

<sup>2</sup>From the Otho S. A. Sprague Memorial Institute, Chicago

<sup>1</sup> For a critical review of the earlier literature on this subject, reference can be made to Kutscher's article in Abderhalden's *Handbuch der Biochemischen Arbeitsmethoden*, 1910, 111-2, 863, and to that of Ackermann 2, p. 1002

<sup>2</sup> Abelous *Compt rend Soc de biol* 1906, 15, 463, *ibid* 1906, 15, 531

<sup>3</sup> Rosenheim *Jour Physiol (Eng)* 1909, XXXIII, 337

<sup>4</sup> Barger and Walpole *Jour of Phys (Eng)* 1909, XXXVIII, 343

<sup>5</sup> Abelous *Compt rend Soc de biol*, 1909, 15, 848, *ibid*, 1909, 15, 596

<sup>6</sup> Bain *Lancet (London)*, 1909, II, 365, *ibid*, 1910, I, 1190, *ibid*, 1911, I, 1409

substances, one soluble in ether, presumably isoamylamine, the other soluble in amyl alcohol and supposedly parahydroxyphenylethylamine. He further found that in several cases of high blood-pressure, these pressor principles were either entirely absent from the urine or in greatly diminished amounts, that on a mixed diet they were in greatest quantity, and greatly lessened if the person whose urine was used was on a vegetable diet. Bain also noted that the bases were absent from children's urine up to the age of 12, and began to be excreted about the fourteenth year. Similar observations had previously been made by Abelous with his urinary extract, which he terms "Uiohypertensine."<sup>5</sup>

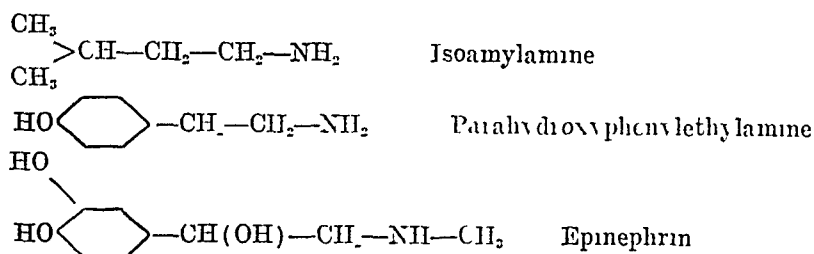
Barger and Dale<sup>7</sup> have shown that the watery extracts of ergot are very similar in melting-point and crystallization to parahydroxyphenylethylamine, and that their physiological action is practically identical. Such a preparation has been put on the market by Burroughs, Wellcome and Co., under the trade name "Tyramine," 0.05 gm of which, when injected into animals, gives quite a pronounced rise in blood-pressure. Dale and Dixon<sup>8</sup> worked on the physiological action of isoamylamine and parahydroxyphenylethylamine, obtaining, in brief, the following results. When injected into cats under ether anesthesia, they both cause a distinct rise in blood-pressure, but much less than epinephrin, the curve rising and terminating more slowly than the latter, with a longer latent period. Of the two, isoamylamine is the less powerful. Both cause an increase in the output of the heart by increasing the rate and amplitude of the beat. Isoamylamine produces a primary depression, parahydroxyphenylethylamine does not. When injected into the circulation, both cause a reflex inhibition through the vagi, with a marked diminution in the rate of outflow from the vessels of the periphery and intestine. Isoamylamine further causes a constriction of the vessels of the lungs, and a slight constriction of the bronchioles. Both cause a contraction of the pregnant uterus and inhibit activity of the non-pregnant organ, the same as epinephrin, although labor was not induced by administration made a week before term. Both substances cause a dilatation of the pupil, protrusion of the eye-ball and secretion of tears. They act when given either hypodermatically or by mouth, and they are absorbed more readily through the alimentary canal than is epinephrin. Their action is not strictly, but mostly, limited to the periphery and there confined to muscles and glands receiving a sympathetic supply. By a comparison of the structural

<sup>7</sup> Barger and Dale Jour Physiol (Eng) 1909, xxxviii, 77

<sup>8</sup> Dale and Dixon Jour Physiol (Eng) 1910, xlii, 25



formula of the bases with that of epinephrin, the similarity can further be noted



Harvey<sup>9</sup> recently reported some interesting effects of the prolonged ingestion of parahydroxyphenylethylamine by animals. He both fed and injected rabbits daily with a 2 per cent solution of this substance over a period varying from eighty to 300 days, gradually increasing the amount. He then killed the animals and found that out of thirty-three twenty had developed renal lesions, in twenty-five there were lesions in the mesial coats of the arteries, and in ten the heart was enlarged and fibrous. His work, however, is open to criticism, in that he fails to state the source of the "parahydroxyphenylethylamine" used in his experiments, the inference being that "Tyramine" was the substance employed. We do not know that chemically this is the same as the supposed parahydroxyphenylethylamine isolated from normal urine.

The significance of the work of Abelous, Bain Harvey and others concerning these pressor bases, is apparent if corroborated. It strongly suggests the possibility that certain diseased conditions which manifest a tendency to high blood-pressure, notably arteriosclerosis and nephritis may be caused by the formation and absorption of putrefactive pressor bases in the intestine. Furthermore, the work which has just been reviewed, would tend to indicate that even in health some formation of pressor bases occurs and it would be plausible enough to assume that under certain conditions of diet or disease the amounts of these substances would be found greatly augmented, and again, that if some method were at hand for measuring them, the amount of putrefactive bases in the urine might be made a useful clinical index of the extent to which this variety of poisoning was going on. The possibility suggests itself also, that an increase in the amount of putrefactive bases absorbed by the body, might be responsible not only for the chronic diseases with high blood-pressure and organic changes in the kidneys and cardiovascular apparatus, but for certain other symptoms as well the causes of which are at present little understood, among which may be mentioned the so-called constipation headaches, asthma and perhaps certain cutaneous disturbances. Much of value in diagnosis, prophylaxis and clinical knowledge would seem to be involved in a study of this problem.

Working toward a solution of these things we should have to go to the beginning and ask, Are these bases, isoamylamine and parahydroxy-

<sup>9</sup> Harvey Path and Bact (Eng.), 1911, vol. 95

phenylethylamine, formed in the intestine? Thus far this question cannot be answered positively, for they never have been isolated from the feces and analyzed as such, although Abelous in attempting to find where his "Urohypertensine" was formed, took 450 gm of intestinal contents and treated it with three times its volume of alcohol. By extracting in the same way as with his method of urine extraction, he was able to obtain a pressor substance, so he assumes that it is formed in the intestinal canal.<sup>10</sup> We must remember, however, that Abelous' "Urohypertensine" has never been identified chemically. Color is given the idea by an experiment performed by Barger and Walpole,<sup>4</sup> who added 17 gm of tyrosin, dissolved in sodium hydroxid, to 300 cc of broth and sterilized. They then infected this with a culture from human feces

TABLE 1—SHOWING METHODS OF EXTRACTION USED, AND EFFECTS ON BLOOD-PRESSURE\*

Specimen No	Amount Used cc	Method	Extracts	Amount Extract, cc	Amount Extract Injected, cc	Effect on Blood- Pressure
1	2,500	Bain	Ether and Amyl	6	2	None
2	2,500	Bain	Ether and Amyl	6	3	None
3	2,500	Bain	Ether and Amyl	6	4	None
4	2,500	Bain	Ether and Amyl	6	5	None
5	2,500	Bain	Ether and Amyl	6	6	None
6	1,000	Abelous (first)	Alcohol	10	10	None
7	1,000	Abelous (second)	Ether	10	10	None
8	1,000	Abelous (first)	Alcohol	10	10	None
9	1,000	Abelous (second)	Ether	10	10	None

\*The specimens of urine were normal and the source was the personnel of the laboratory.

and allowed it to putrefy at 37° C for four days, together with the same quantity of broth with no tyrosin added, as a control. By extraction, a substance was obtained from the former which resembled parahydroxyphenylethylamine in its physiological effects.

The next question presenting itself is, If these bases are formed in the intestine what are their effects in the organism? Are they absorbed as such in amount sufficient to cause symptoms, and do they remain as such in their circulation through the body, finally to be excreted unchanged in the urine? Some light has been thrown on this by the work of Ewins and Laidlaw,<sup>11</sup> who fed parahydroxyphenylethylamine to dogs (0.5 gm to an 8 kilo dog) and were able to recover from the urine but 25 per cent of the parahydroxyphenylacetic acid which was theoretic-

<sup>10</sup> Abelous. *Journ de physiol et path gén*, 1909, xi, 34.

<sup>11</sup> Ewins and Laidlaw. *Jour of Physiol (Eng)*, 1910, xli, 78.

cally possible. They then perfused the substance through a dog's liver, and after two hours no trace could be obtained, but 70 per cent of the possible amount of parahydroxyphenylacetic acid was recovered, showing that the liver had the power to change the base in its circulation through it. By perfusion through the uterus, 0.08 gm of crystalline oxyphenylacetic acid was obtained, which fact would tend to show that either the muscles of the uterus or those of the blood-vessels were able to transform the amine into the corresponding acetic acid.

In order to attack these questions, certain preliminary work seemed necessary, and we decided to proceed along the following lines: (1) To confirm if possible, the finding of these pressor substances in putrid meat and urine, (2) to ascertain the relative amounts of the bases in the urine of healthy individuals on different diets, and the amounts in various diseased conditions, and for facilitating the latter to devise if possible, a method for estimating the quantities of these substances in the urine, which would be simple enough for use with a series of cases and not too elaborate for the clinical laboratory as ordinarily equipped.

We accordingly attempted to obtain the two bases from putrid meat using the method of isolation employed by Bayer and Walpole which briefly is as follows:

One kilo of meat (beef) was stripped of its tendon and fat, ground up, transferred to a large bottle fitted with a perforated cork, with tube to allow the escape of gases, and placed in an incubator at 37 C to putrefy. The meat was not inoculated with any organisms. After eight days when the mass had partially liquefied it was removed and made acid with dilute HCl, and the proteins coagulated in a steamer at 100 C. The mass was then filtered and the filtrate evaporated in vacuum to a thick syrupy consistency. This was then thoroughly mixed with sand and extracted with acetone, the acetone solution was evaporated and the residue shaken with chloroform. The chloroform solution was extracted by means of dilute aqueous HCl, which was then made alkaline with dilute NaOH and extracted repeatedly with ether. By dehydrating the ethereal solution with anhydrous sodium sulphate and adding an anhydrous ethereal solution of oxalic acid, a white precipitate occurred, which was collected on a filter, dried and dissolved in distilled water or physiological salt solution. This represented the alleged ether soluble principle, isoamylamine. The alkaline residue left after the ether extraction was washed with amyl alcohol to remove all other bases, the aqueous solution then made slightly acid with dilute HCl, and again alkalinized with sodium carbonate and extracted with amyl alcohol twice. In this manner the base parahydroxyphenylethylamine should be separated, dissolved in the amyl alcohol. The alcohol was now removed by distillation and the residue dissolved in distilled water for injection.

We were enabled thus to obtain two solutions which had the effects on blood-pressure ascribed to them by Dale and Dixon, namely a rise, with the added observation that when given in large amounts they caused an immediate fall in pressure the animal taking three or four deep inspirations, followed by an immediate cessation of respiration and heart-beat.

We then attempted to obtain from the urine such a pressor substance according to the method employed by Abelous. He first used an alcoholic extract, evaporating 1,000 cc of urine on the water-bath almost to dryness and taking up the residue with 500 cc of 95 per cent alcohol. After standing and filtration, the alcohol was evaporated on the water-bath and the remaining liquid made slightly alkaline with sodium bicarbonate and injected into dogs in doses of 10 cc. Abelous later in

TABLE 2—SHOWING EFFECTS ON BLOOD PRESSURE OF URINARY EXTRACTS FROM PATIENTS ON VARIOUS DIETS AND IN VARIOUS ABNORMAL CONDITIONS

Specimen No	Name	Condition of Patient	Am't Urine 24 hrs, cc	Amount Used, cc	Condition of Urine	Reaction	Diet	Extracts	Amount Injected, cc	Effect on Blood-Pressure
10	Mr. M	Perme Anemia	1,200	1,000	Normal	Acid	Meat Free	Ether	3	None
11	Mr. K	Gastric Ulcer	3,000	1,000	Normal	Acid	Beef, Eggs and Cereals	Amyl	3	None
12	Mr. D	Neurasthenia	1,100	1,000	Normal	Acid	Mixed	Ether	2	None
13	Mr. H	Gastric Ulcer	1,500	1,000	Normal	Acid	Mixed	Amyl	3	None
14	Mr. S	Leukemia	1,700	1,000	Normal	Acid	Mixed	Amyl	4	None
15	Mr. K	Gastric Ulcer	2,200	2,000	Normal	Acid	Mixed	Ether	5	None
16	Mr. L	Arthritis	2,500	1,000	Normal	Acid	Beef, Eggs and Cereals	Amyl	3	None
17	Mr. L	Arthritis	2,200	1,000	Normal	Acid	Mixed	Ether	4	None
18	Mr. L	Arthritis	2,650	1,000	Normal	Acid	Mixed	Amyl	2	None
19	Mr. L	Arthritis	2,650	1,000	Normal	Acid	Mixed	Ether	3	None
20	Mr. W	Cystitis	?	1,000	Bacteria, Pus Cells	Alk	Mixed	Amyl	3	None
21	Mr. L	Tubes	?	1,800	Bacteria, Pus Cells	Alk	Mixed	Ether	4	None
22	Mr. W	Arthritis	2,250	1,000	Normal	Acid	Largely Meat	Amyl	4	None
23	Mr. W	Tubes	2,250	1,300	Bacteria, Pus Cells	Alk	Mixed	Ether	3	None
24	Mr. B	Cirrhosis	2,000	1,500	Normal	Acid	Mixed	Amyl	5	None
								Ether	4	None
								Amyl	4	None

\*The amount of extract in each instance was 6 cc, and the method was the author's modification of Abelous' and Runge's methods.

order to obtain a purer extract modified the method as follows. 1,000 cc of normal urine was saturated with  $\text{HgCl}_2$ , let stand for some hours and filtered. The mercury was removed with  $\text{H}_2\text{S}$  and the filtrate evaporated on the water-bath to about 12 cc. This was taken up with 300 cc of absolute alcohol, shaken and filtered. The filtrate was evaporated until no more alcohol remained, the residue was now made alkaline with bicarbonate of soda and at the end with a solution of soda

and extracted several times with ether. To the ethereal solution was added a solution of oxalic acid in ether, which produced a white precipitate, this was dried on a filter over sulphuric acid, dissolved in 10 c c of distilled water and used for injection. We followed literally both of the above methods, so far as the none too exact description of Abelous permitted using the saphenous vein of dogs for injection, but were unable to obtain a rise of blood-pressure in several trials.

Attention was then turned to the method employed by Bain. He first extracted the urine directly with ether after rendering it alkaline to litmus. Then making it acid with HCl and again alkaline with sodium carbonate, he extracted with amyl alcohol, but later in order to avoid certain colloid substances which interfered with the ether extraction he found the following method to be preferable and it was used by us.

Urine to the amount of 2,500 c c from persons on a mixed diet was thoroughly shaken with 45 per cent of blood charcoal, which, he states, removes not only the colloid substances but the bases as well. This was filtered and the bases removed from the charcoal by boiling with dilute HCl. This mass was again filtered, the acid filtrate rendered alkaline with NaOH, and extracted ten times with ether. It was then made acid with HCl and alkaline with sodium carbonate and extracted with amyl alcohol twice. Both the ether and amyl alcohol extracts were then shaken with dilute HCl and the acid solutions evaporated almost to dryness on the water bath. The excess of acid was removed in a desiccator over soda-lime, and the residue made neutral and taken up in 6 c c of distilled water. Two to 3 c c of this solution was used for each injection.

Although we extracted some ten specimens of urine by this method, in none of them were we able to obtain any pressor substance in either the ether or the amyl alcohol extracts.

In order to obviate any loss of substance which might occur during the extraction of large bulks of urine, we somewhat modified the previous methods of extraction using from 1,000 to 2,000 c c of urine, which we evaporated in vacuum at 40 C to about 75 c c. In some instances 25 per cent phosphoric acid was added in quantity sufficient to prevent any volatile amines going over, in others the acid was not used. The residue was taken up with 300 c c of absolute alcohol, filtered and the filtrate evaporated until all the alcohol had passed off. The solution was then made alkaline with NaOH and extracted with ether, the method of Bain being followed from this point. In none of ten urines did we obtain a pressor substance by this method.

As the urines in the first series were obtained from the personnel of the laboratory, and the others from hospital patients on a mixed diet we sought to explain our inability to get any of the characteristic bases on the ground that perhaps there had not been enough meat in the diets. Accordingly, we placed in the hospital a young man 24 years of age, who was normal in every particular, so far as could be judged from physical examination and laboratory findings, and gave him a diet consisting

largely of meat. During this time he was constipated by administrations of opium. A specimen of his urine before the meat diet was started was extracted and extracts made from daily twenty-four-hour specimens following. On the fifth day a cathartic was administered, and the patient put on a meat-free diet, the urine being collected and extracts made as

TABLE 3—SHOWING EFFECT ON BLOOD-PRESSURE OF URINARY EXTRACTS FROM A NORMAL INDIVIDUAL ON A MEAT AND MEAT-FREE DIET

No. Urine	Amt. Urine 24 Hrs., cc	Amt. Urine Used, cc	Condition of Urine	Reaction of Urine	Method of Extraction	Extracts Made	Amount of Extract, cc	Amt. of Extract Injected, cc	Effect on Blood-Pressure	Diet
21	1,600	1,000	Some phosphates, otherwise normal	Acid	Our	Ether	6	4	0	Mixed
25	1,600	1,000		Acid	Modified	Amyl	6	4	0	
				Acid	Our	Ether	6	4	0	
					Modified	Amyl	6	4	0	
26	2,400	2,200	Normal	Acid	Our	Ether	6	4	0	In 24 hrs 400 gm meat, 3 eggs, clear soup, cream vegetables
					Modified	Amyl	6	4	0	
27	1,750	1,000	Normal	Acid	Abelous'	Ether	10	8	0	In 24 hrs 400 gm meat, 3 eggs, clear soup, cream vegetables
28	2,550	1,500	Normal	Acid	Bain	Ether	6	4	0	In 24 hrs 400 gm meat, 3 eggs, clear soup, cream vegetables
						Amyl	6	4	0	
29	1,950	1,000	Normal	Acid	Our	Ether	6	4	Very slight rise 0	In 24 hrs 400 gm meat, 3 eggs, clear soup, cream vegetables
					Modified	Amyl	6	4		
30	2,050	1,100	Normal	Acid	Our	Amyl	6	4	0	Meat-Free
					Modified	Ether	6	4	0	
31	2,100	1,000	Normal	Acid	Our	Ether	6	4	0	Meat-Free
					Modified	Amyl	6	4	0	
32	2,000	1,200	Normal	Acid	Our	Ether	6	4	0	Meat-Free
					Modified	Amyl	6	4	0	

\*1 Extracts of two days added together

before. In one sample the method of extraction employed by Bain was used; in another Abelous' method, while in the rest our modification of Bains and Abelous' methods was employed. As will be seen by the accompanying table (Table 3) in only one instance was there any rise of blood-pressure obtained by injections in dogs, and that so small as to be without significance.

TABLE 4—SHOWING THE AMOUNTS OF AMINO SUBSTANCE IN THE URINE AND URINARY EXTRACTS UNDER VARIOUS CONDITIONS AND ON DIFFERENT DIETS, AS MEASURED BY THE RÖNCH-SIL MUTARI FORMAMIN TITRATION METHOD

No Urine	Condition of Patient	24 hr Urine, cc	Diet	Formalin Titration on Urine		Formalin Titration on Extracts				Amount of Urine Extracted cc	Action on Blood-Pressure
				Cc N/10 NaOH for 1,000 cc Urine	Gms in 1,000 cc $\text{NH}_3$	Gms $\text{NH}_3$	Cc N/10 NaOH	Amyl Extract	Gms $\text{NH}_3$		
10	Peric Anemia	1,200	Meat Free	205	369	0005	3		006	1,000	0
11	Gastric Ulcer	3,000	Beef, Eggs and Cereals	124	222	002	1 32		022	1,000	0
12	Neurasthenia	1,100	Mixed	265	477				030	1,000	0
13	Gastric Ulcer	1,500	Mixed	40	072				039	1,000	0
14	Leukemia	1,700	Mixed	112	200	002	1 2		012	1,000	0
15	Gastric Ulcer	2,200	Beef, Eggs and Cereals	178	320	019	11 0		019	2,000	0
16	Arthritis	2,500	Mixed	540	972	0			007	1,000	0
17	Arthritis	2,200	Mixed	206	370	002	1 2		010	1,000	0
18	Arthritis	2,650	Mixed	180	324				015	1,000	0
19	Arthritis	2,650	Mixed	210	378				006	1,000	0
20	Cystitis	1,200 (?)	Mixed	4,580	8 24	001	6		029	Alkaline Urine	0
21	Arthritis	2 250	Mixed	120	216	001	8		007	1,000	0
22	Tubes	?	Mixed	1,240	2 23	0005	3		028	Alkaline	0
24	Normal	1,600	Mixed	560	1 00	013	7 4		027	1,800	0
25	Normal	1,600	Mixed	520	93	013	7 4		022	1,000	0
26	Normal	2,400	Meat	220	396	009	5 1		037	1,000	0
27	Normal	1,750	Meat	240	432	010	6 0		021	2,200	0
28	Normal	2,550	Meat	200	360	001	0 6		007	1,000	0
29	Normal	1,950	Meat	280	504	015	8 5		027	1,500	0
30	Normal	2,050	Meat Free	200	360	009	5 4		036	1,000	Slight Rise
31	Normal	2,100	Meat Free	170	306	009	5 4		036	1,000	0

In all the above experiments small dogs of about 6 kilos weight have been used in the physiological tests the animals etherized, trachea exposed and cannula attached to ether bottle inserted, blood-pressure taken from the carotid and recorded on the revolving drum. In some instances the cord was cut in the cervical region and respiration kept up artificially.

We have extracted some thirty-seven urines for these pressor substances, and with none of our preparations has any such rise of pressure as described by Abelous and Bain occurred. There are several ways in which these negative results might be interpreted. (1) The substances are not in the urine, or (2) they occur in such small quantities as to be negligible in the amount of urine used for extraction, or (3) the technic on our part has been faulty. As we have gone over every step carefully in the methods employed, varying at times some detail where it occurred to us a mistake might be possible on account of the inaccuracy of the methods as given, it is hard for us to draw this last conclusion. It is possible, however, that results of different kinds might be obtained if one had to rely exclusively on the extraction methods as given by the various authors in their reported articles, for not only are they difficult to interpret but woefully lacking in details which are essential to careful work. In considering whether these pressor bases are present in normal urine, as the work of Abelous and Bain would tend to show, it should be recalled that we are starting out with the assumption that the substances are formed in the intestine and excreted as such in the urine. Consequently we should consider the question as to whether these bases, even if present in the bowel, may not be changed in the organism during their circulation through it, into compounds which, when excreted in the urine, may fail to give a pressor effect. The results obtained by Ewins and Laidlaw by perfusing parahydroxyphenylethylamine through various organs, as reported above would tend to show that such is the case.

As to the third possibility, it is recognized by all who have attempted to isolate these bases from the urine, that they occur in extremely small quantities. Indeed Barger and Walpole<sup>4</sup> evaporated some 30 liters of urine and were unable to get enough of a pressor substance to identify it chemically. Again the methods of extraction employed are not only tedious so far as practical purposes are concerned, but somewhat uncertain, as it is a well-known fact that there are many ether soluble bases in urine and from the lack of means of identification at hand we are unable to state the composition of a given extract. It occurred to us at the start that animal injection for an estimation of different degrees of blood-pressure in different extracts, is faulty. For not only do the conditions affecting each animal at the time of injection have to be taken into consideration, but also the size of the animal and the number of injections into each. Because in using two or more extracts on the same animal, the second probably would not give so great a rise as the first even though it



contained a pressor substance in greater amount, on account of fatigue and other factors. Consequently the present methods did not seem to us suited for clinical work, assuming, as we did, that such pressor bases are present in the urine, since we required a more rapid and accurate means of estimation in order to carry out any further work. Reasoning along these lines, it was suggested by Dr. Woodyatt that the Rönchese-Malfatti<sup>12</sup> formalin titration for total amino and ammonia nitrogen might serve as an available means, as already applied by Henriques and Sorenson<sup>13</sup> for a variety of purposes. We found that 0.05 gm of tyramine (which corresponds closely physiologically and chemically to parahydroxyphenylethylamine) gave with this test a titration figure of 0.3 cc (N/10) NaOH. We accordingly tested by this method several specimens of urine before extraction and also the extracts from these same specimens, which supposedly contained the pressor bases. The technic employed was as follows:

A specified amount of the urine or extract was put in a small flask or beaker and diluted with 50 cc of distilled water. In a second container was put 5 cc of formalin (40 per cent formaldehyd) with 10 cc of distilled water. To each of these solutions was added 3 drops of phenolphthalein. They were then treated with N/10 NaOH until the first permanent pink color appeared. The solutions were now added one to another, the pink color disappearing. The combined solution was then titrated with N/10 NaOH until the first permanent pink appeared and the reading was taken. The number of cc of N/10 NaOH required for this was used empirically as a comparative index for the total amount of ammonia and amino nitrogen present in the urinary extracts. For instance, if it required 6 cc of N/10 NaOH to bring the pink color to the combined solutions in one extract and 8 cc in another, we figured that there would be more basic N substance in the latter and that animal injection might show a correspondingly great increase in blood pressure, and that thus eventually we might for clinical purposes obviate the necessity of the physiological test. As a further comparison we multiplied the number of cc (say 6) empirically by .0018 which would give .0108 as the number of grams of titratable base in terms of NH<sub>3</sub> in 5 cc of urine or extract. In 100 cc there would be .2160 gms and the amount for 1,000 cc of urine, or more, may readily be estimated from this percentage.

Although the results obtained by the use of the above method were by no means constant we had in almost every case some formalin titratable substance. We therefore submit a table, showing the amount present in the various urines, and also the amount in the extracts of each urine in terms of N/10 NaOH, reckoned for 1,000 cc of urine, as that was the amount used for most of our extractions. We offer this merely as an interesting possibility. Furthermore, we had intended to check up and compare the results obtained by this method with those obtained by animal injection, but since we were unable to obtain in any of the urines a pressor substance which could be demonstrated by the latter means, no comparison was, of course, possible.

We hope soon to report some further work on the presence of pressor bases in the feces.

12 Hoppe Seyler. *Ztschr f physiol Chem*, 1909, lxi, 6, 499.

13 Henriques and Sorenson. *Ztschr f physiol Chem*, 1909, lxi, No 1, 27.

## CONCLUSIONS

1 Two pressor substances, corresponding to isoamylamine and parahydroxyphenylethylamine (as identified by Barger and Walpole), may be isolated from putrid meat

2 The formation of these substances in the intestine, by bacterial putrefaction of proteins, is probable, but whether they are absorbed and remain unchanged in the organism to be excreted as such in the urine, is problematical

3 The isolation of certain pressor substances from normal urine, as reported by Abelous and Bain, could not be confirmed by us

4 Further, there is no definite chemical proof that these urinary pressor substances are isoamylamine and parahydroxyphenylethylamine

5 Further work on the presence of these pressor bases in the organism, and their possible relation to certain cases of high blood-pressure, would seem highly desirable. For this purpose some practical means for the identification and measurement of these substances must be developed. The formalin-titration method, applied to suitably prepared urinary extracts, offers an interesting possibility in this connection

I desire to express my extreme appreciation to Dr Joseph L. Miller for the instigation of this work and for his valuable assistance at all times during the course of it, to Dr S. A. Matthews for his aid in the physiological experiments, and to Dr H. Gideon Wells and Dr Rollin T. Woodyatt for suggestions and help

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## A CRITICISM OF TWO PERCUSSION METHODS FOR THE DIAGNOSIS OF THE ENLARGED THYMUS

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Bednar (1852), Vogel (1856), von Mayr (1862) described briefly the percussion signs of the enlarged thymus. Sahl<sup>1</sup> (1882) first made an extensive study of these signs on living subjects. Blumenreich<sup>2</sup> (1902) investigated the signs on dead subjects, comparing the shape of the percussion dulness with the exposed portion of the gland as revealed at the subsequent autopsies. The principles for determining the thymus by percussion, as laid down by Sahl and modified and amplified by Blumenreich, hold to-day. They have the confirmation of anatomical fact. There have been advanced, however, two percussion methods for the recognition of the enlarged thymus which rest on anatomical hypotheses. The present paper is a discussion of the anatomical conditions underlying these two methods.

While the methods of Sahl and Blumenreich are directed at the more exact determination of the outline of percussion dulness, the methods in question — those of Jacobi<sup>3</sup> and Boggs<sup>4</sup> — aim at the determination of a movable dulness at the thymus site. Jacobi and Boggs' methods, then, are based on the hypothesis that the thymus is a movable organ.

The theory of the mobility of the thymus is not new. It had had advocates at least since the time when Giawitz (1888) became the exponent of the mechanical theory of thymic asthma. Some of the adherents to this theory of thymic asthma (Rehn<sup>5</sup>) have explained the dyspnea on the ground that during expiration the movable thymus was pushed up into the neck, during inspiration sucked back into the thorax against the trachea obstructing it in a valvelike manner. Other exponents of this theory have held that owing to the connection of the thymus to the thyroid, the thymus may be drawn upward into the narrow outlet of the thorax by dorsal flexion of the head (the hypothesis of Boggs' percussion

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<sup>1</sup> From the Pathological Department, New York Foundling Hospital.

1 Sahl, Hermann. Die topographische Percussion im Kindesalter, J. Dalph. Beitr., 1882.

2 v. Blumenreich, Robert. Ueber die Thymus Dämpfung. Virchows Arch. f. path. Anat., 1900, clx, 35.

3 Jacobi, Abraham. In Modern Clinical Medicine, edited by Abraham Jacobi. D. Appleton & Co. New York, p. 37. Diseases of Children (Footnote).

4 Boggs, T. R. Percussion Signs of Persistent or Enlarged Thymus. THE ARCHIVES INT. MED., 1911, viii, 659.

5 Rehn, L. Die Thymusstenose und der Thymustod. Arch. f. klin. Chir., 1906, lxxx, 468, Cited by Gebelli, Beitr. z. klin. Chir., 1910, lxx, 20.

method) and, there becoming wedged, swells and exerts pressure. During their operations for the relief of thymic asthma, Rehn, Erhardt, Alsberg and others have seen the thymus bulge into the neck in expiration and disappear into the thorax in inspiration, and lastly, Rehn has watched the up and down movements of the thymus in the thorax by means of the fluoroscope. Jacobi and Boggs alone, so far as we know, have based a method of thymus diagnosis on thymus mobility.

Then respective methods hypothecate different movements of the thymus. While that of Jacobi presupposes a movement in an antero-posterior direction, away from and back against the anterior chest wall, the method of Boggs presupposes an up and down movement in the long direction of the sternum. For the diagnosis of the enlarged thymus, Jacobi<sup>6</sup> places his subject on the back and percusses the normal thymus site for resonance, on the supposition that the enlarged thymus has fallen away from the anterior chest wall. Then, with his subject lying face downward, he percusses the same area from underneath for dulness, on the theory that the thymus has fallen back against the anterior chest wall. The change in the character of the percussion note coincident with this reversal in posture, Jacobi regards as characteristic of the thymus gland.

Boggs<sup>4</sup> uses a more complicated procedure to determine the enlarged thymus. He puts his subject into the sitting position, depresses the chin toward the sternum and outlines the dulness "behind the manubrium and in the interspaces." He then retracts the head toward the midline of the back and repeats the percussion. If the former dulness is that of the thymus, it will now be found "to have shifted upward, often as much as an interspace or more."

Boggs explains the anatomical conditions underlying his method in these words:

The gland is attached by one or two suspensory or thyrothymal ligaments to the lower poles of the corresponding thyroid lobes. Otherwise the thymus is but slightly bound to the surrounding tissues and is free to move in the direction of the long axis of the sternum. If it is borne in mind that the thyroid gland is in turn connected to the hyoid bone and from this to the mandible by more or less continuous ligaments and muscles, it is seen that a ligamentous chain extends from the anterior part of the lower jaw obliquely downward and backward to the thymus.

Turning now to the consideration of this theory of thymus mobility, we may say at the outset that there are certain relations of the thymus to adjacent structures which force themselves on the attention of the operator in the course of an autopsy, because they obstruct his progress. When for instance, the sternum is lifted up by its lower end and a view of the interior of the thorax obtained from underneath, it is necessarily

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<sup>6</sup> Jacobi, Abraham. *Therapeutics of Infancy and Childhood*. J. B. Lippincott Co. Philadelphia, Pa. 1908.

seen that a fascial attachment exists between sternum and thymus, because this attachment must be freed before the sternum can be removed. If an attempt is made to lift the thymus out of the thorax, the pericardium together with the heart and the diaphragm is lifted also. It is often difficult to locate the plane of cleavage between the thymus and the pericardium so close is their union, and when in the separation of the two the left innominate vein is reached, it is often accidentally cut away with the thymus, so firmly adherent is it to the thymus. In order to become convinced of the truth of these statements it is necessary merely to remove a thymus at autopsy.

The thymus is contained in a fascial sac, the capsule. Between the outer surface of the sac and the thymus a loose attachment exists. Surgeons<sup>7</sup> (König, Rehn, Alsberg and others) in their operations for the relief of thymic asthma have made use of this fact, that when the capsule of the thymus is opened a large part of the thoracic portion of the thymus can be drawn up into the neck. But between the outer surface of this sac and the thoracic structures a different condition exists. In front the capsule is attached to the sternum loosely. At the sides, it is joined to the mediastinal pleura. Behind it is bound to the pericardium so closely that it may be said to be united to that structure, it is entangled about the left innominate vein and closely joined to the sheaths of the great vessels. Fascial prolongations may connect it with the trachea, bronchi and pulmonary veins. Above, the sac is in continuity with the deep cervical fascia. It is important to note also in this connection that when the thymus is much enlarged the attachments of its capsule become more extensive. For example, in recorded cases in which the thymus has reached the diaphragm, the capsule has been found adherent there. While, then, the thymus may be regarded as loosely fastened inside its own capsule, the capsule itself must be thought of as most intimately attached, not to one thoracic structure alone, but to all thoracic structures. These attachments could not be more universal nor those situated posteriorly much firmer, were they of an inflammatory origin. It is therefore difficult to regard the thymus as a movable organ.

The thymus, then, according to Boggs, is "attached" by "thyrothymal ligaments" to the thyroid, and is in a "ligamentous chain" connected with the "mandible." Since the thymus is in closer attachment to the pericardium than to the thyroid, and since the pericardium is in turn attached to the diaphragm, and the diaphragm to the liver, would it not be as reasonable to include the liver in this ligamentous chain attached to the mandible? Or, in reply to the argument that the thymus must be drawn up with the thyroid, since it is attached by thyrothymal ligaments to the

<sup>7</sup> Holtz, Gerhard. Die Ursachen des Thymustodes. Beitr. z. Klin. Chir., 1907, 14, 509.

thyroid, would it not be as reasonable to say that this might occur, were not the liver present to weight the thymus down? The term ligament may be a proper term for the connections between the thymus and the thyroid, but the word gives to us an exaggerated impression of the actual condition. The connection between thymus and thyroid exists only in the deep cervical fascia, which is stronger about the trachea than elsewhere. Nor can we agree with Boggs in his statement that the thymus is not overlapped by the lungs, for the lateral and inferior parts of the thymus are always overlapped by the lungs. We have seen more than once a small thymus completely covered by the lungs. The description which Boggs gives of the anatomical conditions supporting his theory seem to us to convey a false impression.

For the same reasons we think that Jacobi's conception of thymus mobility in the anteroposterior direction is untenable.

We have investigated the truth of these methods in a series of twenty-nine autopsies performed at the New York Foundling Hospital. In each case a window was cut in the upper part of the manubrium, the pleura was not ruptured. The thymus could be inspected through this window. With the body in a dorsal position, we invariably found the thymus in close apposition to the sternal wall. It could not be pushed back easily. This finding is exactly opposed to Jacobi's theory. On performing Boggs' procedure exactly as performed by Boggs himself on the living subject, it was possible to observe that the thoracic portion of the thymus does not move. In some of the cases, by extreme retraction of the head, the upper, superficial parts of the thoracic portion of the thymus might be stretched upward a distance of 3 mm. But the middle parts remained essentially immobile. By exerting a powerful traction upward on the hyoid bone, the entire thymus could be pulled upward 2 or 3 mm, but it carried with it the diaphragm, pulling the costal margins in.

But even if the thymus were movable and could be drawn up, the lower border of thymus dulness would not be shifted upward, provided the lung margins remained fixed. Boggs evidently conceived of the thymus as hung, biblike, in *front* of the lungs, else how could he assume that the lower border of thymus dulness varies with the degree of elevation of the thymus? In reality the lower and lateral parts of the thymus lie *behind* and below the lung margins which, separated from each other above meet at the level of the second or third rib, demarcating a V-shaped area of thymus tissue between them. This uncovered V-shaped area lies immediately behind the manubrium and represents the percussion area. The lower limit of the thymus dulness does not, therefore, coincide with the lower border of the thymus, but corresponds to the margins of the lungs. The idea that the lower border of thymus dulness rises when the thymus is drawn upward is actually no more reasonable than would be

the idea that the waistcoat opening would be shifted upward if the shirt is drawn upward by the neckband. It is true that a part of the shirt, previously below the level of the waistcoat opening, by this procedure would be raised above it and come into view. So parts of the thymus previously below the level of the V-shaped opening formed by the lung margins would be drawn up into the percussion area but the position of the lower border of thymus dulness would not be changed so long as the lung margins remained stationary.

How are the observations of Rehn, Alsberg and others of the movements of the thymus occurring during their operations to be explained? Our answer to this question must be theoretical, for we have never seen the phenomenon described by them. We should suppose that the movement consisted chiefly in a suction of the cervical portion of an enlarged thymus into the thorax during inspiration, with its return during expiration—that such is the case rather than an expulsion of the thoracic portion of the thymus into the neck. Since in obstructive dyspnea some of the movable structures of the neck are pulled down toward the cavity of the thorax, among them the trachea with the thyroid it could be conceived that the cervical part of the thymus capsule might also be carried down into the thorax. This appears to have been actually so in a case reported by Rehn. As a matter of fact, it is comparatively easy at autopsy, by catching the thoracic portion of the thymus with the forceps, to draw down the cervical portion into the thorax. It may also be that the thymus can be displaced inside its own capsule, stretched from one end of it to the other by the changes in intrathoracic pressure. In violent dyspnea the thoracic organs as a whole may to an extent rise and fall with the movements of the diaphragm.

If the methods of Jacobi and Boggs cannot be explained on the basis of a movable thymus, how may they be explained otherwise? The variables in the upper thorax are the lungs. We know that Boggs' procedure may increase the anteroposterior dimensions of the thorax at the level of the manubrium. To compensate for a loss of space somewhere else the lung margins may be forced further upward over the thymus. If this advance of the lung margins upward occurred as the result of Boggs' maneuver it would explain his "shift of the thymus dulness" upward.

Our conclusion, then, from an anatomic study of autopsy cases is that percussion methods of the thymus, based on the theory of thymus mobility, are founded on a false anatomical hypothesis.

## PELLAGRA IN ILLINOIS

### CONDENSED REPORT OF ILLINOIS PELLAGRA COMMISSION

(Concluded from page 168)

CASE 6—*Pellagra in a Man Suffering from Senile Dementia Death in Three Months without Symptoms of Central Neuritis*

*History*—A J B, white male, farmer, 66 years of age Nothing is known of his previous history He was admitted to the Peoria State Hospital from the Soldier's Home at Quincy, Illinois, Nov 1, 1910 At that time he was obese and somewhat feeble, with exaggerated knee-jerks but flexor plantar reflexes Mentally he showed complete loss of memory for recent events, was irritable and peevish Considered to be suffering from senile dementia

In June, 1911, he was found to have a well-marked pellagrous eruption on the hands, with some desquamation From this time he rapidly lost flesh and became more and more dull, although the specific symptoms of pellagra disappeared, and he died without any definite symptoms so far as can be discovered of central neuritis, Sept 11, 1911

At the autopsy evidences of healed tuberculosis in the lungs were found and the liver was described as being much engorged, its appearance suggesting almost a nutmeg condition, but its weight was only 44 ounces The heart was thin and flabby and no definite changes were noted in the kidneys

#### MICROSCOPIC EXAMINATION

*Liver* Microscopically the liver shows slight increase in the amount of fibrous tissue the capillaries are engorged, especially near the intra-lobular veins and there are small scattered islets of small-celled infiltration in the portal canals Fatty degeneration is extremely marked, involving the outer layer of cells of each lobule and ceasing a little less than half way to the central vein With osmic acid all the lobules are clearly marked out by the black stain

*Kidneys* The kidneys show marked increase of fibrous tissue and a few small subcapsular cysts The vessel walls are thickened and in many places show hyaline changes Small hemorrhages are present in some glomeruli In the medullary rays many of the tubules appear to have undergone a hyaline change and to be completely occluded This material suggests a lardaceous change but it does not show the characteristic staining reactions

The suprarenals show marked fatty degeneration especially in the zona reticularis where every cell contains large fat droplets Fatty changes are present but less marked in the fasciculata and still less so in the glomerulosa Small hemorrhages are present in all layers and the central veins are engorged with blood

The *pancreas* shows moderate increase of fibrous tissue and a few small hemorrhages

*Nervous System* In the nervous system the changes are extreme Similar chromatolysis involving especially the giant pyramidal cells of the precentral cortex to those found in the other cases as well as fatty degeneration of a most widespread character are present But besides this there is a marked overgrowth of glial cells especially the satellite and perivascular cells The arteries are markedly thickened and in this case there is a very moderate degree of small-celled infiltration of the vessel sheaths thus forming a decided contrast to the other case examined Further study of this nervous system is needed before expressing any opinion on the findings but it cannot be regarded as an uncomplicated case of pellagra

A B—It should have been stated on page 147 that the work on Protozoa was performed by Captains Siler and Nichols



CASE 7—*Pellagra in a Man Suffering from Chronic Alcoholism Right Hemiplegia with Paraphasia and Left Paraparesis Later also Weakness of Left Side*

*History*—C. C., white male, ice handler. The patient has been healthy but a heavy drinker for years. In September, 1910, at the age of 51 it was noticed that his memory was defective and he seemed dazed and confused. This was thought to be due to alcoholism and he was sent to the Peoria County Poor Farm. His apparently stupid condition continued until early in January, 1911, when he became irritable, noisy and seemed to be worried.

*Examination*—He was admitted to the Peoria State Hospital January 25, 1911, when he was found to have arteriosclerosis, a slight right hemiplegia with exaggeration of reflexes on that side, paraphasia, and paraparesis of the left side.

In April, 1911, he developed pellagrous lesions of both hands with some diarrhea. At the same time he began to lose flesh. The eruption had disappeared by early June but he continued to fail in general health. At the beginning of June he became very weak and seemed to have had some further cerebral insult, the left side being said to be weakened. At this time the reflexes were markedly increased on both sides and there was a bilateral Babinski phenomenon. He continued to lose strength and weight rapidly and died July 30, 1911, without having had any convulsive phenomena.

*Necropsy*—The necropsy was performed seventeen hours after death and showed as follows. Marked atrophy of the cortex, especially in the frontal regions, but no gross lesion even when sectioned after hardening. Dense adhesions obliterating the pleural and pericardial sacs, with chronic posterior mediastinitis. Hypertrophy of the left ventricle with atheroma of coronaries. Liver engorged with blood and firmer than normal. Spleen and other viscera engorged. Kidneys showed no definite changes. No ulceration found in the intestines.

#### MICROSCOPIC EXAMINATION

*Liver*. Microscopically the liver shows no thickening of the capsule but there is a small celled infiltration of circumscribed character here and there in the portal canals in places almost outlining a lobule. The capillaries are engorged, especially towards the central veins. Fatty degeneration is slight but where present is in the cells at the periphery of the lobules. It is less in amount than that of any of the cases so far studied, a careful search being necessary to find the areas in which it occurs.

*Spleen*. The spleen shows increase of fibrous tissue with small hemorrhages.

*Intestines*. Small intestine shows infiltration of the mucosa and submucosa with leukocytes and in places small hemorrhages.

*Nervous System*. The examination is as yet very incomplete but the following facts are noteworthy.

*Nerve Cells*. These have so far been studied with thionin staining only in the anterior regions of the brain. Chromatolysis of axonal type is very marked in the giant cells of the precentral region. Many of the larger pyramidal cells also show similar change. This process is more marked in the sections in the anterior portions of the precentral gyri where many of the smaller elements are also affected. Pigmentary degeneration of a fatty nature staining well with Scharlach is extremely wide spread and involves many of the smaller cells as well as the larger ones.

*Glia and Vessels*. The glia nuclei are moderately increased, the satellite cells are quite numerous and there are often rows of nuclei along the walls of the vessels. The vessels themselves show considerable hyaline degeneration of the intima with hyperplasia of the adventitia. Scharlach staining shows that many of the cells in this position contain fat droplets. The perivascular spaces, however, are not infiltrated with lymphocytes or plasma cells and there is nothing in the picture to suggest a parasymphilitic condition.

*CASE 8—Unhappy Marriage with Poor Adjustment Spells of Moping and Mutism Intestinal Symptoms Shortly Followed by Manic Excitement, and Three or Four Weeks Later by Stomatitis and Pellagious Dermatitis Increasing Restlessness, Severe Diarrhea with Rapid Emaciation and Death in Two Months*

D S, white female, a housewife and baker by occupation, 42 years of age

*Family History*—Incomplete The mother and her relatives are said to have been weakly and to have died young No insanity known

*Personal History*—Nothing known of her earlier life She was married in 1896 and has never been happy According to her husband she was always shiftless and careless about her household duties and has been cranky, nervous and dissatisfied The patient's relatives blame the husband for the discontent and general unhappiness She is said to have been quarrelsome with her neighbors, inclined at times to mope and refuse to talk There have been three children, two normal, while the third died at the age of three weeks In 1909 the husband left her and states that she did not succeed with the business, owing to her shiftlessness

She has always lived in Havana, Mason County, Ill., and has worked in the bakery business owned by her husband since marriage There has never been any financial difficulty and the patient has always had plenty to eat

*Present Illness*—In January, 1911, the patient began to suffer with gastrointestinal disturbance About the middle of April she is said to have become "maniacal" At the beginning of May a sore throat developed, the tongue and gums being very red, and at the same time her hands became discolored and "bruised," due as was thought to the use of mechanical restraint

She was admitted to the Peoria State Hospital June 2, 1911, when she presented marked coppery pigmentation with roughness and scaly desquamation of the skin of the dorsum of the hands and forearms, extending upwards to the junction of the middle and upper thirds This area showed a well-marked line of demarcation and was entirely symmetrical on the two sides The skin over the knuckles was rough and heaped up but without fissures The tongue was reddened and denuded at the tip and there was severe diarrhea with loose, offensive stools

*Examination*—The examination was rendered unsatisfactory by the extreme restlessness of the patient She was constantly talking, clapping her hands and singing, showing marked distractibility, with sound and motor speech associations When alone she was constantly busy, tearing up her bed and bedding, jumping out of bed, showing all the appearances of a happy excitement The excitement was readily increased by the presence of others and in answer to question she said she "felt fine," "I am an angel" Her "husband was extremely rich," had a "white automobile with gold trimmings," etc No evidence of hallucinosis was obtained Distractibility rendered orientation impossible

Physical examination was incomplete but the knee-jerks were found to be exaggerated and it was suggested that the pupils did not react well, but there were no other facts on which to base any diagnosis of general paralysis of the insane

The extreme restlessness continued with but little sleep Diarrhea persisted and emaciation and exhaustion were progressive Death occurred July 8 about two months after the onset of the first symptoms

Permission for a post mortem examination was refused

#### IV ANIMAL EXPERIMENTATION

Much time has been devoted to the attempt to transmit pellagra to lower animals On the advice of the late Dr. Howard T. Ricketts, rhesus monkeys have been used in the main All results have been entirely

negative, so that it will suffice to summarize the experiments which have been performed

1 Twelve monkeys have been inoculated either subcutaneously or intraperitoneally with *defibrinated blood* obtained from patients suffering from pellagra in the recent or subsiding stage (In one of these the case was probably not pellagra )

2 Three monkeys have been injected subcutaneously with the filtrate obtained by passing the blood of pellagrins through Pasteur or Berkefeld filters

3 Two monkeys were given hypodermic injections of the *blood serum* obtained from human pellagrins Of these one was first filtered through a Berkefeld filter

4 Three monkeys received injections of *cerebrospinal fluid* obtained from pellagrins Of these one was procured post mortem and given subcutaneously, in the other two the fluid was drawn during life, one being injected into the subcutaneous tissues and the other into the peritoneal cavity

5 One monkey has received subcutaneous injections of an *emulsion of spleen* obtained from a human pellagin

6 Four monkeys have been *fed for long periods on a strict corn diet*, and of these one has also received extremely mouldy corn meal while one has been fed with a bacillus (Strain 67), obtained from the stools of pellagrins showing certain agglutinating relations with pellagrous blood-serum, and more fully detailed above

7 One monkey has been fed with extremely moldy corn meal together with bacillus No 67

8 One monkey and one guinea-pig were inoculated subcutaneously with bacillus No 67

9 Twenty-three guinea-pigs were inoculated or fed with extracts from moldy corn meal

10 One monkey and one guinea-pig were inoculated with a bacillus isolated from the blood of a human pellagin

11 One kitten received per rectum an emulsion of a stool from a pellagin containing numerous living amebas

12 Three monkeys have been fed with the fecal matter of pellagrins containing living amebas

At this point it would be well to call attention to a physiological condition occurring in rhesus monkeys which does not appear to be generally known During early life the skin of the perineum is white or bluish-white, but on reaching puberty these animals develop a vivid red color in this region similar to that which is well known in the closely related species of baboon This erythema varies in degree from time to time and seems to bear some relation to the menstrual functions When

at its height it is accompanied by marked edema and involves not only the perineum, but also the genital folds extending sometimes upwards to the lower part of the abdomen, downwards on the inner surfaces of the thighs and around the anus to the root of the tail

By a curious coincidence a number of our monkeys developed this erythema, as indicated in our preliminary report, at a more or less definite interval after they had been inoculated, and we were consequently inclined to attach some significance to its occurrence. The condition is very much more marked in the female than in the male, but we have seen some examples in the latter which were very distinct. Apparently one of the main reasons for its occurrence not being more generally known is that the animals, in captivity, frequently die before reaching maturity.

#### V. COMPLEMENT FIXATION EXPERIMENTS

This work was carried out by Dr. J. Frank Waugh and is briefly abstracted by him as follows:

The technic of the test was that described by Noguchi. An alcoholic extract of the liver from a pellagrin and a similar extract of the liver from a monkey which was killed forty-one days after the appearance of the erythema referred to above, were used as antigens.

Fifty-two sera from pellagrins which were tested with an alcoholic extract of human pellagra liver as antigen resulted as follows: thirty-four, or 65% per cent, gave a mildly positive reaction, twenty-eight, or 54% per cent, were negative. Five normal sera from persons who came in daily contact with the pellagrous patients proved to be negative, with the exception of one that was mildly positive. Thirteen specimens of blood from cases other than pellagra were used as controls. Among these were four sera from luetic patients, one of which gave a mildly positive reaction.

Fourteen sera from pellagrins were tested with monkey-liver antigen. Six gave a positive reaction, eight being negative.

Both antigens were used on eighteen sera from monkeys. Seven of the eighteen monkeys had been inoculated with blood from well-marked cases of pellagra. Four of the sera gave a positive reaction with both antigens while three were negative. Four of the specimens were from animals having a well-marked perineal erythema, but which had not been inoculated. With human antigen none was positive with monkey antigen two were positive and two negative. Seven of the specimens were from monkeys considered normal. One gave a positive reaction with both antigens, while six were negative.

Inhibition to hemolysis was only partial in all the positive cases. In no instance was there a strong reaction such as we get in lues when a luetic liver extract is used as antigen.

While the results of these tests are strongly suggestive further work will be necessary to demonstrate whether or not a specific reaction is present.

## VI CUTANEOUS ANAPHYLACTIC TESTS WITH CORN EXTRACTS

This work was carried out by Arthur D Hirschfelder, M D, Baltimore, whose complete report follows

The zeistic history of pellagra, as enunciated by Lombroso and v Babes,<sup>5</sup> that "Pellagia is to be considered as a chronic and periodically occurrent intoxication, which is due to a specific substance formed in more or less spoiled corn," is founded more on statistical evidence than on clear-cut experiments Lombroso and subsequent workers, it is true, have isolated from corn toxic products which have some action on the nervous system of dogs, and v Babes and Manicatide claim to have prevented this action in rabbits by injection of blood serum from a cured pellagrin On the other hand, comparatively little has been done to test the sensitiveness of pellagia patients themselves to substances derived from corn

If the zeistic theories of pellagia were correct, it seemed possible that the chronic corn intoxication presupposed by Lombroso and v Babes might be accompanied by a condition of anaphylactic hypersensitiveness to products derived from corn, or perhaps only from spoiled corn The present series of observations was undertaken, accordingly, with a view to determining the presence or absence of such sensibility

Since, v Pirquet<sup>6</sup> has demonstrated that the cutaneous reaction affords the most delicate means of testing anaphylactic sensitization in man to tuberculin and other substances Quite recently, Rufus Cole and W S Thayer were able to demonstrate hypersensitization to buckwheat infusion in a case of fagopyrismus reported by H L Smith<sup>7</sup> They found that if a drop of buckwheat extract were rubbed into a portion of the skin from which the epidermis had been removed by scratching, an urticarial wheal and general constitutional symptoms appeared within half an hour

Since certain analogies between pellagia in man and fagopyrismus in animals had been recognized for decades, it seemed possible that a similar anaphylaxis to corn products might be met with in pellagrins It seemed possible also that such a reaction, if positive, might be of importance for the diagnosis of pellagia

In these observations, cutaneous tests were made with substantially the same technic employed by v Pirquet, except that corn extracts were substituted for tuberculin in making the test

5 Lombroso, C Die Lehre von der Pellagra Aetiologische, klinische, und prophylaktische Untersuchungen Transl by H Kurella Berl, 1898, v Babes, V, and Sion, V Die Pellagra Nothnagel's Handb d spez Path u Therap Wien, 1901

6 v Pirquet, C Tuberkulindiagnose durch cutane Impfung Berl klin Wchnschr, 1907

7 Smith, H L Buckwheat Poisoning, with Report of a Case in Man THE ARCHIVES INT MED, 1909, III, 350

The procedure was as follows 20 gm of corn was extracted with 50 cc of ether, alcohol, 10 per cent NaCl, or 0.2 per cent NaOH. The extract was filtered and 1/10 vol 5 per cent carbolic acid added to the clear filtrate, so as to give it a content of 0.5 per cent carbolic acid. The ethereal extracts were allowed to evaporate at 46 C, until the odor of ether had disappeared.

The site chosen for the test was an area on the patient's wrist which was subject to pellagrous pigmentation, thickening or desquamation, and, in the most cases, was bare, so as to be exposed to the action of light. A drop of the extract to be tested was placed on the skin and a pinhead area of epidermis beneath the drop was excoriated by the torsion of a *Van Piquet* stylet. Into this excoriated area the extract was rubbed with a glass rod. A series of epidermal punctures were made in this way in a line across the wrist, with another line of duplicate punctures above them. In each series there were a pair of controls, in which only the pure NaCl or NaOH solution or alcohol was placed on the skin.

Within half an hour after the puncture, a small red or sometimes blanched areola, and occasionally a small papule, formed about the site of inoculation, but in only one case did these exceed 5 mm in size, and no differences could be noted between the areas about the punctures with corn extracts and the controls. The reactions in sites which were nearest the middle of the forearm were often slightly more marked (areolas about 1 mm larger than the rest), but these reactions were always quite as marked with the control fluids as with the extracts, and hence were of little significance.

The reactions, which were regarded as negative in all cases, consisting of simple traumatic reactions, were watched for about half an hour, and the sites of inoculation were again inspected three hours, twenty-four hours and forty-eight hours later, as well as at frequent intervals between.

Extracts were made from samples of good corn, spoiled corn taken from the Arkansas Insane Asylum at the time of a pellagra outbreak, and a sample of spoiled corn containing *Aspergillus fumigatus*. The extracts of the latter were filtered through a Berkefeld filter in order to avoid the danger of inoculating the aspergillus. Other extracts were made from the apparently excellent corn meal used at the Peoria State Hospital for the Insane at the time that pellagra was breaking out throughout the asylum, and when a number of cases of acute pellagra were developing. Tests were made on thirteen cases of well-defined pellagra diagnosed by Dr. George A. Zeller and confirmed by Drs. Singer and MacNeal of the Illinois Pellagra Commission.

These reactions were all negative. Just before leaving Peoria, a sample of spoiled corn was obtained which had been rejected by the asylum and sent out to the hog farm over a year previously. Extracts of

this corn were inoculated into six patients with subacute pellagra. The effects were observed for three hours after inoculation, but were uniformly negative.

In order to determine whether the presence of antibodies formed in a previous attack of pellagra might cause the reaction to be given by persons who had been afflicted with the disease in the previous year but who were free from symptoms at the time of inoculation, observations were made on seven such patients. In all cases the results were negative.

The results of these tests, therefore, render it improbable that pellagra is due to or accompanied by a condition of hypersensitiveness of the individual to products derived from good or from spoiled corn.

I take pleasure in expressing my thanks to Dr. George A. Zeller and the Illinois Pellagra Commission for placing at my disposal the patients and laboratory of the Peoria State Hospital as well as to Dr. Carl Alsberg of the Bureau of Plant Industry for furnishing samples of good and spoiled corn.

#### VII. DIETARY STUDIES

In view of the alleged relations between pellagra and deficiency in food both as regards quantity and quality the following points have been submitted to study:

1. The nutritive value of the general diet supplied to the inmates of the Peoria State Hospital, the institution where the largest number of cases of pellagra developed.

2. A rough estimate of the relative amounts of meat used in the different state hospitals in comparison with the prevalence of pellagra.

3. The quality of corn in use at the state hospitals and elsewhere. In connection with this experiments have been made to determine the toxicity of some samples of moldy corn.

4. A comparison of the effects of an excessive corn diet with one which was free or practically so from maize products. An analysis of the excessive corn diet has been carried out and a rough comparative estimate of the nutritive value of the corn-free diet used in this experiment was also made. It was unfortunately impossible under existing conditions to make this estimation more complete.

1. For the study of the general diet at the Peoria State Hospital a group of representative patients, about fifty-three in number, was selected. The quantities of food which they actually consumed during a period of seven days were accurately determined by weighing the total food served and food left uneaten. Representative samples of the food used were taken and analyzed for protein, fat, carbohydrates, mineral matter and phosphorus. The energy values were calculated. The results of this study are summarized in Table 14. As far as possible the samples were composited. Thus the samples designated animal foods represent foods chiefly of animal origin, i. e., meats and cheese, vegetable food foods chiefly of vegetable origin, i. e., fruits, cereals, potatoes and other vegetables, bread, breads, cake, etc. mixed foods, food containing appreciable

TABLE 14 — SUMMARY OF GENERAL DIET

	Weight of Food Used		Protein		Carbohydrates		Fat (Ether Extract)		Fuel	Ash (Mineral Matter)		Phosphorus	
	Kilos	Per cent	Quantity, gms	Per cent	Quantity, gms	Per cent	Quantity, gms	Per Cent	Calories	Per Cent	Quantity, gms	Per Cent	Quantity, gms
20,039 Animal foods	58.53	13.99	8,188.35	3.59	2,101.23	12.33	7,216.75	2.12			1,240.84	0.162	94.82
20,040 Vegetable foods	374.81	1.87	7,008.95	16.26	60,944.11	0.37	1,386.80	1.09			4,085.43	0.041	153.67
20,041 Bread	134.17	8.49	11,391.03	57.40	77,013.58	0.63	845.27	1.19			1,596.62	0.095	127.46
20,042 Mixed foods	77.31	1.96	1,515.28	15.11	11,081.54	1.42	1,097.80	0.97			749.91	0.036	27.83
20,043 Coffee and tea	294.36	0.04	117.74	0.99	2,914.16	0.03	88.31	0.06			176.62		
20,044 Milk	21.07	3.12	750.98	1.96	1,193.87	2.56	616.19	0.74			178.12	0.094	22.63
20,045 Butterine	12.48	0.44	54.91			98.21	11,608.61	3.30			411.84	0.014	1.75
20,047 Syrup	26.44	0.16	42.30	76.17	20,139.35	0.07	18.51	1.25			330.50	0.007	1.85
20,050 Salt	0.65							99.75			648.37		
Total in food used			29,069.54		175,987.84		22,278.24				9,418.25		430.01
20,048 Waste food	34.15	3.18	1,053.97	19.62	6,700.23	2.73	932.30	1.37			467.86	0.064	21.86
20,049 Waste food	19.71	3.48	685.91	21.77	4,200.87	3.24	638.60	1.64			323.24	0.047	9.26
Total in waste food			1,771.88		10,991.10		1,570.90				791.10		31.12
Amount actually consumed <sup>1</sup>			27,297.66		164,996.74		20,707.34				8,627.15		398.89
Average per man per day			73.51		414.34		55.77				23.23		1.07
Average per kilo body weight <sup>2</sup>			1.10		6.62		0.83				0.35		0.016

1 Net amount for 7 days, 53 1/21 subjects

2 Average weight of subjects, 67.1 kilos



quantities of both vegetable and animal materials, i e, puddings. The other samples consisted of the materials their names indicate. By waste food is meant the food left on the tables and plates, which was in such condition that it could not be separated. This was collected and analyzed and its nutritive values deducted from those of the total food used in computing the quantities of food and nutrients actually consumed.

The distribution of the nutrients among animal and vegetable foods has been calculated and is summarized in Table 15. Such classification, however, is not absolute, for the samples were taken from cooked foods which contain materials derived from both sources. Nevertheless, the figures probably represent the true character of the diet.

TABLE 15—DISTRIBUTION

Laboratory No	Food Materials	Fresh Food			Dry Substance			Protein	
		Quantity kilos	Per cent of Total	Per Man per Day gms	Quantity kilos	Per cent of Total	Per Man per Day gms	Quantity gms	Per cent of Total
20,039	Animal foods	58.53	5.84		18.75	7.92		8,188.35	28.5
20,044	Milk	24.07	2.40		2.74	1.16		750.98	2.5
Total animal foods		82.60	8.24	222.44	21.49	0.08	57.86	8,939.33	30.0
20,040	Vegetable foods	374.81	37.38		73.42	31.30		7,008.95	24.0
20,041	Bread	134.17	13.38		90.85	38.39		11,391.03	39.0
20,043	Coffee and tea	294.36	29.35		3.30	1.39		117.74	0.4
20,047	Syrup	26.44	2.64		20.53	8.68		42.30	0.1
Total vegetable foods		829.78	82.75	2,234.61	188.10	79.49	506.56	18,560.02	63.0
20,042	Mixed foods	77.31	7.71		15.04	6.36		1,515.28	5.0
20,045	Butterine	12.48	1.24		11.34	4.79		54.91	0.2
Total mixed foods		89.79	8.95	241.81	26.38	11.15	71.06	1,570.19	5.2
20,050	Salt	0.65	0.06	1.75	0.65	0.27	1.75		
Total food used		1,002.82	100.00	2,700.62	236.62	100.00	637.22	29,069.54	100.0
20,049	Waste food	53.86	5.37	145.05	15.12	6.39	40.73	1,771.88	6.0
Amount actually consumed		948.96	94.63	2,555.57	221.50	93.61	596.49	27,297.66	93.9

2 When the work of this commission was planned it was hoped that it would be possible to study the general diet at each hospital in the same manner as that actually carried out at the Peoria State Hospital. This, however, has unfortunately been found to be impossible owing to lack of time and assistance. The findings at Peoria detailed in the last section revealed deficiency in the amount of animal protein served to each patient. Since the main source of this constituent was provided in the meat it was thought that a comparison of the meat supplied to each institution

daily per capita might afford some sort of basis for conclusions as to the quantity of animal protein at the other hospitals. In Table 16 is shown the average daily amount of meat in ounces supplied to each individual including both patients and employees.

In considering these figures it must be remembered that the weights represent almost entirely uncooked and undressed meats. Secondly, the employees, while being absolutely fewer in numbers, receive relatively much larger amounts of meat. It would be quite impossible to determine exactly what the relative proportion is, and since the proportion of employees to patients is approximately the same in the different institutions it is quite permissible to make comparisons on the figures as they

## NUTRIENTS—GENERAL DIET

Carbohydrates			Fat			Fuel Value		Ash			Phosphorus		
Quantity gms	Per cent of Total	Per Man per Day gms	Quantity gms	Per cent of Total	Per Man per Day gms	Per cent of Total	Per Man per Day Calor's	Quantity gms	Per cent of Total	Per Man per Day gms	Quantity gms	Per cent of Total	Per Man per Day gms
2,101.23	1.19		7,216.75	32.39				1,240.84	13.17		94.82	22.05	0.26
1,193.87	0.68		616.19	2.77				178.12	1.89		22.63	5.26	0.06
3,295.10	1.87	8.87	7,832.94	35.16	21.09	11.63	319	1,418.96	15.06	3.82	117.45	27.31	0.32
60,944.11	34.63		1,386.80	6.22				4,085.43	43.37		153.67	35.74	0.41
77,013.58	43.76		845.27	3.79				1,596.62	16.95		127.46	29.64	0.34
2,914.16	1.66		88.31	0.40				176.62	1.87				
20,139.35	11.44		18.51	0.08				330.50	3.51		1.85	0.43	0.01
161,011.20	91.49	433.61	2,338.89	10.49	6.30	72.58	1,991	6,189.17	65.71	16.67	282.98	65.81	0.76
11,681.54	6.64		1,097.80	4.93				749.91	7.96		27.83	6.47	0.07
			11,008.61	49.41				411.84	4.37		1.75	0.41	0.01
11,681.54	6.64	31.46	12,106.41	54.34	32.60	15.79	433	1,161.75	12.33	3.13	29.58	6.88	0.08
								648.37	6.88	1.75			
175,987.84	100.00	473.94	22,278.24	100.00	60.00	100.00	2,743	9,418.25	100.00	25.36	430.01	100.00	1.16
10,991.10	6.25	29.60	1,570.90	7.05	4.23	6.38	175	791.10	8.40	2.13	31.12	7.24	0.08
164,996.74	93.75	444.34	20,707.34	92.95	55.77	93.62	2,568	8,627.15	91.60	23.23	398.89	92.76	1.07

stand. It will be noted that there is a big increase in the Peoria figures between the first three years and the fourth. In part this was due to an actual increase in the amount of meat supplied to each patient, but it is also in part to be explained by the fact that during this period many of the attendants who used to live off the grounds of the hospital have been required to take up their residence within the institution.

The actual analysis of the food at the Peoria State Hospital was made during the fourth period, July, 1910, to July, 1911, so that this figure,

82, must be used as a basis of comparison. From the results of the analysis we are forced to conclude that the animal protein constituent of the dietary provided at all the state hospitals, with the possible exception of that at Jacksonville is certainly small.

The period of observation has been too short and the data are obviously too incomplete to justify any conclusions. It may, however, be noted that the number of cases of pellagra has diminished at Peoria and Dunning coincidently with increased meat supply, whereas they have apparently increased at Elgin with diminished meat. This may be a matter of pure coincidence, but is worthy of further investigation.

TABLE 16.—AVERAGE DAILY AMOUNT OF MEAT IN OUNCES SUPPLIED TO EACH INDIVIDUAL, INCLUDING BOTH PATIENTS AND EMPLOYEES

	July, 1907 to July, 1908	July, 1908 to July, 1909	July, 1909 to July, 1910	July, 1910 to July, 1911	Average
Peoria	53	58	59	82	63
Anna	113	109	106	98	106.5
Chester	64	50	45	64	56
Elgin	71	77	69	59	69
Jacksonville	106	109	113	105	108
Kankakee	87	78	80	82	82
Watertown	82	79	84	83	82
Dunning	65	65	66	75	68

3 Samples of corn meal from eight institutions were analyzed chemically for moisture and acidity. For comparison similar determinations were made on nineteen other samples of corn meal from various sources. The results are shown in Table 17. The acidity has been calculated on a moisture-free basis and is expressed in terms of N/10 NaOH solution required to neutralize the alcoholic extract of 100 grams of meal.

The official standard in this country requires that "maize meal, corn meal or Indian corn contain not more than 14 per cent of moisture. An Austrian investigator states that sound corn and corn meal should require less than 30 cc—generally 15 to 25 cc—N/10 NaOH solution to neutralize the alcoholic extract of 100 grams of the meal.

Judged by the moisture content, acidity, presence of molds and other microorganisms, and the presence of insects the corn meal used in the state institutions is, on an average, of very good grade. It was found to be of better quality than the corn meal purchased in the open market in Urbana and in Alabama, and also better than six samples from Italy. Cultures were made from all parts of the samples for molds. No quantitative determination of the molds present was attempted. Of all samples only one No. 20006, obtained from Anna, contained no molds. Both

moisture and acidity of this sample were the lowest of all the twenty-seven samples examined

The changes brought about by the action of molds on corn meal were studied with special reference to the formation of toxic substances

For this purpose portions of corn meal were sterilized and inoculated from pure cultures of molds. After a good growth had been secured the moldy meal was extracted with 90 per cent alcohol for three to four hours at a temperature of 65 to 70 C. The alcohol extract was filtered off (using the centrifuge when necessary) and evaporated *in vacuo* over sulphuric acid to dryness. The dried residue was next extracted with absolute alcohol and the extract filtered. This filtrate was likewise evaporated to dryness *in vacuo* over sulphuric acid. The residue thus obtained was extracted with water, the water solution made alkaline with sodium carbonate and extracted with ether. The ether solution was allowed to evaporate spontaneously. As this is essentially the Stas Otto method for the extraction of ptomaines, the residue from the ether extract should contain the toxic substances originally present. Other residues and fractions were also tested, however, and in those cases in which toxic products were found it was in fractions other than the last residue described.

TABLE 17—AVERAGE ACIDITY AND MOISTURE CONTENT OF CORN MEAL FROM VARIOUS SOURCES

	Acidity, cc N/10 NaOH	Mois- ture Per Cent
Corn meal from state institutions (8 samples)	40.7	13.99
Corn meal from local grocery store (3 samples)	51.3	12.58
Slightly spoiled meal from Kankakee (1 sample) (not used as food for patients)	60.3	15.69
Good meal from Alabama (3 samples)	65.1	11.74
Damaged meal from Italy (6 samples)	112.1	15.76
Damaged meal from Alabama (3 samples)	113.0	11.83
Very badly spoiled and moldy meal (3 samples)	174.7	65.06

Of the five molds (three varieties of *Penicillium*, one *Mucor* and one *Monascus purpureus*), only one, *Monascus purpureus* gave a toxic substance when grown on corn meal in pure form.

Another sample of meal on which a blue green species of *Penicillium* had grown, but which had become contaminated by other organisms, was very toxic.

Some further experiments to investigate the presence of toxins in corn were carried out by Captains Nichols and Siler.

After taking some corn meal mush from a boiler just before it was served and letting it stand in a sterile Petri dish for two days, we found it covered with slimy, reddish growth, which proved to be that of *Bacillus mesentericus fuscus*. This organism and strains of *Penicillium glaucum*, *Aspergillus flavus* and *Diplodia* recovered from musty corn, which were

kindly furnished us by Professor Burrill of the University of Illinois, were used in trying to discover any evidence of toxins. Moist corn meal was put in large flasks, sterilized and inoculated with these organisms. After a rich growth was obtained, it was scraped off with some of the corn meal, diluted with water, thoroughly shaken, centrifuged or filtered and the clear liquid used for injection of rabbits and guinea-pigs. A large number of rabbits were used, and injections were given subcutaneously, intraperitoneally and intravenously. The results were uniformly negative. When corn-meal mush was allowed to decompose naturally and a similar extract used for injections, the animal died, but the result is readily attributable to putrefactive organisms. Feeding experiments with infected corn were started, but soon given up, as it was found that the animals refused to eat the corn after the first day and died of starvation.

4 *Feeding Experiments*—At the suggestion of Captains Nichols and Siler, two cottages, with a capacity of about sixty patients, were filled with non-pellagrous patients of the chronic class. Careful stool examinations were made for protozoa. One cottage was then placed on a generous corn diet—approximately 16 ounces of corn food-stuffs per day. The other cottage, containing about sixty patients, was placed on a corn-free diet of the same general nature. These diets were continued for one year and the patients were placed directly in charge of Dr. Watkins of the hospital staff, who followed them with great care. Dr. Watkins' report included a description of the daily diet in each cottage. This detail may be seen in the complete report. In addition, a personal chart was kept for each patient, noting carefully the following points:

- 1 Examination of the feces
- 2 Semi monthly weights
- 3 Mental conditions as to mania and stupor
- 4 Physical conditions, with special attention to diarrhea, gastritis, stomatitis, and skin lesions

This experiment was carried out during the entire year, and on September 15, 1910 these facts are noted. Nearly all the patients gained gradually on both wards from September to March or April, when they gradually fell off during the hot weather until they averaged about the same weight as on the same date the preceding year. On the corn diet twenty-five patients gained in weight during the year, twenty-nine lost and four remained unchanged. The average loss and gain on both cottages was from 2 to 3 pounds.

There were sixteen patients on the corn diet who suffered with diarrhea during the year, while only ten on the corn-free diet suffered from the same malady, and there were more cases of constipation on the corn-free diet cottage than on the corn diet cottage.

During the year, the corn diet cottage showed four cases of pellagra, with one death from the disease. The corn-free cottage showed five cases of pellagra, with two deaths from the disease. During the year there were four suspected cases of pellagra on the corn-free diet cottage.

Of the four suspected cases, the examination of the stools was negative as to active amebas, but in two cases there were encysted amebas and encysted flagellates. One patient had a mild erythema of the dorsum of the hands during January, 1910. This patient gained 7 pounds during the year and at present shows no symptoms of pellagra.

In a general way, the results of this experiment may be summarized as follows:

FEEDING EXPERIMENTS IN TWO COTTAGES DURATION ONE YEAR

	Patients	Cases of Pellagra	Suspects
Corn diet cottage	59	4	1
Corn-free diet cottage	58	5	5

It is evident from these results that an extensive corn diet did not favor the production of pellagra. Cases developed in each ward in practically the same proportion, and this proportion agrees in general with that found throughout the institution, which was also on a corn-free diet. It is not claimed that this experiment absolutely disposes of all forms of the corn theory of the production of pellagra, but it is difficult to reconcile the results with the ordinary theories incriminating corn as a causative factor in the production of the disease.

The analysis of the corn diet was conducted similarly to that of the general diet with the exception that a separate sample was made of all foods derived from maize. The quantities of foods and nutrients consumed are summarized in Table 18, and the distribution of the nutrients among animal and vegetable foods in Table 19. There were fifty-six patients in this group.

No complete study of the corn-free diet was made, but the quantities of food consumed by the group taking this diet fifty-seven in number, were determined for two days. These figures are given in Table 20.

Before any definite conclusions can be drawn from such studies as this it is obviously necessary that further investigations be made with accurate metabolism experiments. It is difficult to judge of the adequacy of the protein content in the above studies because very little information

TABLE 18—SUMMARY CORN DIET

Laboratory No	Food Materials	Weight of Food Used, Kilos	Protein		Carbohydrates		Fat (Ether Extract)			Ash (Mineral Matter)		Phosphorus	
			Per Cent	Quantity, gms	Per Cent	Quantity, gms	Per Cent	Quantity, gms	Fuel Value, Calories	Per Cent	Quantity, gms	Per Cent	Quantity, gms
20,051	Animal foods	73.56	10.37	7,628.17	4.68	3,442.61	11.30	8,312.28		1.97	1,449.13	0.113	83.12
20,052	Vegetable foods	268.41	2.03	5,448.72	13.61	36,530.60	0.73	1,959.39		1.18	3,167.24	0.046	123.47
20,053	White bread, etc	100.46	9.52	9,563.79	56.63	56,890.50	2.87	2,883.20		1.25	1,255.75	0.116	116.53
20,054	Mixed foods	86.08	1.94	1,669.95	14.44	12,429.05	0.69	593.95		0.65	559.52	0.032	27.55
20,055	Coffee and tea	475.19	0.03	142.56	1.32	6,272.51	0.02	95.04		0.05	237.60		
20,056	Milk	89.07	3.10	2,761.17	4.87	4,337.71	2.67	2,378.17		0.71	632.40	0.093	82.84
20,057	Butterine	13.84	0.53	73.35			87.25	12,075.40		3.66	506.51	0.016	2.21
20,058	Corn foods	283.69	4.05	11,489.44	20.47	83,603.44	2.75	7,801.18		1.57	1,453.93	0.105	297.87
20,059	Syrup	10.72	0.16	17.15	76.00	8,117.20	0.05	5.36		1.05	112.56	0.006	0.64
20,061	Salt	0.35								99.77	349.20		
Total in food used				38,794.30		211,654.52		36,104.27			12,723.87		734.23
20,060	Waste food	148.47	3.10	4,602.57	20.48	30,406.66	3.56	5,285.53		1.20	1,781.64	0.062	92.05
Amount actually consumed <sup>1</sup>				34,191.73		181,247.86		30,818.71			10,942.23		642.18
Average per man per day				87.22		462.37		78.62	2898		27.91		1.64
Average per kilo body weight-				1.39		7.37		1.25	46.2		0.45		0.026

1 Net amount for seven days, fifty six subjects

2 Average body weight, 62.7 kilos

is available regarding the food requirements of the insane It is permissible, however, to make the following suggestions

1 The protein content of the general diet is probably sufficient but is certainly not excessive

2 This diet is chiefly vegetable in nature, much more so than the average American dietary It is conceivable that a deficiency in animal protein may predispose to pellagra

3 An excess of corn products in the dietary of fifty-seven patients continued for a period of one year did not result in the development of more pellagra than in a similar squad of fifty-seven patients whose diet contained no corn, other conditions being equal

4 The quantities of nutrients, energy, and mineral substances ingested per man per day by the patients receiving the corn diet were adequate but not excessive The scanty data at hand seem to show that the corn free diet was at least equal in nutritive value to the corn diet

5 The quality of corn meal supplied to the state hospitals is of high grade

6 The growth of the commoner varieties of mold in pure culture on corn meal does not give rise to great toxicity

#### VIII SIMULIA IN ILLINOIS

Owing to the importance placed on the buffalo gnat as a possible carrier of the disease by Sambon, the Commission invited Prof Stephen A Forbes, State Entomologist, to make an investigation in this field. He very kindly consented, and presented an admirable report It is only possible here to outline a part of his findings The reader who is interested is respectfully requested to consult the monograph published by the commission for Professor Forbes' full report

#### GENERAL DESCRIPTION

The buffalo gnats or black flies, all species of the genus *Simulium*, are small, two-winged insects with thick, hump-backed bodies and sharp piercing and sucking beaks They vary in length, according to species, from 1/25 to 1/6 of an inch—1 to 4.5 mm They are notorious for the immense numbers in which they swarm in early spring, especially along the larger streams, and for the painfulness of the punctures made by the females (the males being inoffensive), and the ferocity and fierceness of their attack They are, generally speaking, more annoying than seriously injurious to mankind, although several deaths have been more or less plausibly attributed to their attack, but to domestic animals, especially to cattle, horses and mules, and even to poultry, they are a terrible and terrifying scourge

As is very commonly the case with blood-sucking diptera, the young or larvæ of these flies are aquatic The eggs are laid in patches on objects under water, the larvæ transform there to pupæ and the pupæ to winged adults, which escape to the surface each in a bubble of air absorbed from the water through the gills of the pupa and stored up under its cuticle.



The larvæ are so abundant locally, under the most favorable conditions, that the water is said sometimes fairly to boil as the winged insects burst from its surface, each in its air bubble

#### NUMBER AND GENERAL DISTRIBUTION OF SPECIES

There are about sixty-five species of this genus in the world. Twenty-five of them have been found in North America and fifteen in the United States. Nine species are known by us to occur in Illinois, and a possible tenth species is represented by an unidentified larva found in Vermilion

TABLE 19.—DISTRIBUTION OF

Laboratory No	Food Materials	Fresh Food			Dry Substance			Protein		
		Quan- tity Kilos	Per cent of Total	Per Man per Day gms	Quan- tity Kilos	Per cent of Total	Per Man per Day gms	Quan- tity gms	Per cent of Total	Per Man per Day gms
20,051	Animal foods	73 56	5 25		20 83	6 96		7,628 17	19 66	
20,056	Milk	89 07	6 36		10 11	3 38		2,761 17	7 12	
Total animal foods		162 63	11 61	414 87	30 94	10 34	78 93	10,389 34	26 78	26 50
20,052	Vegetable foods	268 41	19 15		47 11	15 75		5,448 72	14 05	
20,053	White bread, etc	100 46	7 17		70 59	23 60		9,563 79	24 65	
20,055	Coffee and tea	475 19	33 91		6 75	2 26		142 56	0 37	
20,059	Syrup	10 72	0 76		8 28	2 77		17 15	0 04	
Total vegetable foods		854 78	60 99	2,180 56	132 73	44 37	338 60	15,172 22	39 11	38 43
20,054	Mixed foods	86 08	6 14		15 25	5 10		1,669 95	4 30	
20,057	Butterine	13 84	0 99		12 51	4 18		73 35	0 19	
20,058	Corn foods	283 69	20 24		107 35	35 89		11,489 44	29 62	
Total mixed foods		383 61	27 37	978 60	135 11	45 17	344 67	13,232 74	34 11	33 76
20,061	Salt	0 35	0 02	0 89	0 35	0 17	0 89			
Total food used		1,401 37	100 00	3,574 92	299 13	100 00	763 09	38,794 30	100 00	98 96
20,060	Waste food	148 47	10 59	378 75	42 08	14 07	107 33	4,602 57	11 86	11 74
Amount actually consumed		1,252 90	89 41	3,196 17	257 05	85 93	655 75	34,191 73	88 14	87 22

County, Illinois, and also abundant in Yellowstone Park. One American species, *S. hirtipes*, found in northern Illinois, occurs in Europe, and another, *S. reptans*, abundant throughout Europe, is reported from Greenland also, but not elsewhere in North America. It is to this latter species, indeed, that the spread of pellagra has been ascribed in Italy.

#### GENERAL FEATURES OF LIFE HISTORY OF ILLINOIS SPECIES

Neither the life histories nor the habits of any of our American species have been sufficiently studied, and the one best known (*S. pictipes*) happens to be of the least interest from our present point of view, since

it has never been known to bite. Our Illinois species differ considerably in distribution, life history and places of most frequent occurrence. Two of them—the so-called turkey gnat (*S meridionale*) and the buffalo gnat (*S pecuarum*) are the species to which southern accounts of these insects usually apply. Although they occur occasionally far to the north, they are southern in their general range and predominant numbers, and have not been found by us in northern Illinois. *S venustum*, the black fly or sand-fly of the northern woods, is, on the other hand, perhaps the most abundant species in the north, although *S vittatum* is frequently found

## NUTRIENTS CORN DIET

Carbohydrates			Fat			Fuel Value		Ash			Phosphorus		
Quantity gms	Per cent of Total	Per Man per Day gms	Quantity gms	Per cent of Total	Per Man per Day gms	Per cent of Total	Per Man per Day Calories	Quantity gms	Per cent of Total	Per Man per Day gms	Quantity gms	Per cent of Total	Per Man per Day gms
3,442.61	1.63		8,312.28	23.02				1,449.13	11.39		83.12	11.32	0.21
4,337.71	2.05		2,378.17	6.59				632.40	4.97		82.84	11.28	0.21
7,780.32	3.68	19.84	10,690.45	29.61	27.27	12.68	428	2,081.53	16.36	5.31	165.96	22.60	0.42
36,530.60	17.26		1,959.39	5.43				3,167.24	24.89		123.47	16.82	0.31
56,890.50	26.88		2,883.20	7.90				1,255.75	9.87		116.53	15.87	0.30
6,272.51	2.96		95.04	0.26				237.60	1.87				
8,147.20	3.85		5.36	0.01				112.56	0.88		0.64	0.09	0.00
107,840.81	50.95	275.10	4,942.99	13.69	12.61	40.50	1,367	4,773.15	37.51	12.18	240.64	32.78	0.61
12,429.95	5.87		593.95	1.65				559.52	4.40		27.55	3.75	0.07
			12,075.40	33.45				506.54	3.98		2.21	0.30	0.01
83,603.44	39.50		7,801.48	21.60				4,453.93	35.00		297.87	40.57	0.76
96,033.39	45.37	244.98	20,470.83	56.70	52.22	46.82	1,580	5,519.99	43.38	14.08	327.63	44.62	0.84
								349.20	2.75	0.89			
111,654.52	100.00	539.94	36,104.27	100.00	92.10	100.00	3,375	12,723.87	100.00	32.46	734.23	100.00	1.87
30,406.66	14.37	77.57	5,385.53	14.64	13.48	14.13	477	1,781.64	14.00	4.55	92.05	12.54	0.23
181,247.86	85.63	462.37	30,818.74	85.36	78.62	85.87	2,898	10,942.23	86.00	27.91	642.18	87.46	1.64

in its company. The first of these is said by Prof. F. L. Washburn to be an annoyance to stock in Minnesota, and the second a torment to mankind. These two species are the commonest ones in northern and central Illinois. We have likewise a fifth species, hitherto undescribed, the larvæ of which are abundant in the Illinois river, and two or three others which occur more sparingly in various parts of the state.

Our species differ also in the number of generations, the two especially southern forms (*S pecuarum* and *S meridionale*) having so far as known but one generation in a year, which reaches the winged stage in early spring, while the two most abundant northern forms (*S venustum* and

*S vittatum*) appear in the winged stage at intervals throughout the summer, and evidently have two or more generations, just how many is not known. *S pictipes* also develops at least two generations.

Some of these species breed mainly in small streams, while others find favorable situations for reproduction in the largest rivers. *S meridionale* and *S vittatum* are examples of the first habit, and *S pecuarum* and *S venustum* of the second. Larvæ and pupæ of all are limited to flowing streams, the larvæ quickly dying, indeed, if transferred to quiet water. They are evidently very sensitive to a deficiency of oxygen and can live as a rule only where the current is swift or where its movement is so interrupted by shallows or by objects lying or growing or suspended in the stream as to produce at least a surface whirl or ripple.

TABLE 20.—COMPARISON OF CORN AND CORN FREE DIETS. QUANTITIES OF FOOD USED, PER MAN, PER DAY, DURING THE FIRST TWO DAYS OF EXPERIMENTS

Kind of Food	Weights of Food Used per Man per Day (gms.)	
	Corn Diet	Corn Free Diet
Animal foods	289.73	301.23
Milk	336.52	352.98
Coffee and tea	1,046.25	1,099.56
Butterine	34.46	45.44
Other foods <sup>1</sup>	1,736.60	1,984.82
Total foods used	3,443.56	3,784.03
Waste foods	366.79	470.70
Amount actually consumed	3,076.77	3,313.33

1 Includes for			
Corn Diet	Gm	Corn Free Diet	Gm
Vegetable foods	671.16	Vegetable foods	983.68
White bread, etc	280.98	White bread, etc	430.88
Mixed foods	169.46	Mixed foods	570.26
Corn foods	635.00		
Total	1,736.60	Total	1,984.82

The larvæ are rather peculiar creatures, with slender cylindrical, maggot-like bodies, thickened and club-shaped at the hinder end, by which they adhere to some submerged object, and with a pair of fan-like clusters of filaments near the mouth. They are commonly grouped in colonies often thickly covering the object to which they are attached. They spin from their mouths silken threads, with which they form a loose network covering the surfaces they occupy, and by means of which they can recover their position if swept away by the current. They move mainly like a measuring worm, with the aid of a sucker near each end of the body. They pupate in a case or nest composed of web spun from the

mouth, and the pupa breathes by a pair of tufted gills extending forward from the open mouth of the case

In the two species whose life histories have been fairly well followed, namely *S. pictipes* and *S. venustum*, about two months elapse in summer between the laying of the egg and the appearance of the winged fly, the egg stage lasting about one week, the larval four weeks, and the pupal three. In colder weather the development proceeds more slowly. As these species hatch from the egg in New York in the first part of May, there is time, at this rate for three successive generations, the last of which hibernates in the larval stage, pupating in April of the following year. We have sufficient data concerning the times of occurrence of the winged black flies in Illinois to bring all but three or four of our species under this category. The single-brooded species appear in the winged stage in central Illinois in April and May, the date of maximum abundance here in two successive years having been about April 25. The farther south one goes and the earlier the spring, the earlier is the swarming time of the gnats. Indeed, we have one report from Louisiana of the appearance of winged buffalo gnats during every month of an unusually mild winter and a consequent failure of the usual spring rush in February and March. Although six of our Illinois species send out summer broods, these are so scanty and scattering that it is difficult to find winged specimens in the field, even by careful expert search, at any time except in spring.

#### BREEDING SITUATIONS OF THE BLACK FLIES

The number of our Illinois species, and the fact of their distribution in all parts of the state, make it practically certain that black flies may be found sooner or later wherever and whenever the somewhat peculiar local conditions required for their breeding are present. These conditions are in the first place, running water continuous through the breeding season, and, in the second place, either a rippling surface or a fairly rapid flow of the stream. It is also necessary that there should be solid objects in the water, not more than a few inches under the surface, on which the eggs may be laid and to which the larvæ may cling. The water must also of course, contain a sufficient supply of the smaller plankton and other organic particles on which the larvæ feed. As they remain attached like plants and cannot search for food, they are dependent on whatever chance brings within reach of the prehensile apparatus about the mouth. The species which breed in rivers find these conditions most general during high water, especially in spring. Then the current of the stream is comparatively swift and strong near the shores, and the marginal overflow reaches to trees and shrubs, stranded driftwood, and the like which create the necessary surface disturbance and at the same time provide places of attachment for the eggs and larvæ. In the smaller

streams, on the other hand, times of flood are less favorable, except where there is a rocky bed, but as the summer grasses grow, dipping into the stream and marginal shrubs droop their twigs loaded with leaves into the water, and as the heavier objects on the bottom of the creeks and rivulets are brought near the surface by the shrinking of the stream, many suitable places may be found here and there for the black fly to deposit eggs and for the young to reach the pupation stage.

Myriads of these insects are sacrificed, as our field notes show when the waters fall, leaving the pupæ exposed and liable to dry out. Small fish and certain carnivorous insects especially caddis worms, devour the larvæ, and their numbers in summer and fall are rarely very great in our latitude. The bottom lands of our principal rivers—the Illinois, the Mississippi, the Ohio and the Wabash—from the middle of April to the middle of May, are almost the only situations in which the black flies may be called a plague. As the swarms of these insects are readily blown about by the wind, they are often carried to considerable distances from their place of origin, and cases are on record in which they must have been borne several miles in this way. The adults are not long-lived, and an outbreak does not ordinarily continue annoying longer than ten days. A storm of wind and rain may, in fact, put an end to it in even less time.

The description of the various species found is necessarily omitted here.

#### POSSIBLE RELATION TO PELLAGRA

To ascertain definitely whether the distribution of black flies in Illinois and the times of their principal appearance, local and general, have any relation to the occurrence and frequency of cases of pellagra would require a very much broader and closer survey of the state, with this point especially in mind, than it has been possible for me to make. With the exception of a part of the data obtained at Havana and Peoria in 1910, those here reported are the product of general miscellaneous collections made during many years, with no thought of any pathological application. They are sufficient, however, to show the common occurrence of black flies throughout the state. Our specimens have come from sixteen counties—five in northern Illinois, eight in central and three in southern—as follows: northern Illinois—McHenry, Carroll, Cook, La Salle and Mercer; central Illinois—Peoria, Tazewell, McLean, Vermilion, Champaign, Mason, Fulton and Green; and southern Illinois—Wabash, Saline and Jackson.

The places and situations of occurrence are such as to warrant the opinion that black flies might be found in larger or smaller number in every county of the state. They would be most abundant, of course, along the larger rivers (and it is only there that they become noticeable as

pests), and the species would differ with the size and character of the streams, and, to some extent, with the latitude

The only attempt I have been able to make toward a comparison of local facts concerning simulum with the local data of pellagra is based on observations made at Bartonville, near Peoria, in the latter part of August, 1910. The location there of the general hospital for the insane, in which pellagra is almost continuously present, gave us reason to examine the surroundings of this institution as carefully as possible, and visits were made to this place by Mr. C. A. Hart on August 29, 30 and 31. In a small stream just north of the hospital grounds at Bartonville, which leaves the bluff on which the buildings stand, passes under the highway and flows eastward through low ground towards the river, simulum larvae were obtained just below the wagon bridge, on the leaves of trailing branches and on other objects in the stream, although none could be found in this stream above the highway. The point at which the black flies were breeding was about a third of a mile in direct line from the hospital buildings. No pupae were seen in the water and no winged flies could be caught by diligent sweeping of the vegetation in that vicinity. Two small streams emerging from shady valleys in the bluffs to the south of the hospital grounds were destitute of simulum larvae.

In Kickapoo Creek, between Bartonville and Peoria, a very few larvae and pupae were found, and a considerable number were taken in favorable places all along Farm Creek near the East Peoria station, across the river from the hospital. These were not in the deeper or wider parts of the creek, but in its very smallest lateral divisions and the shallowest margins of the riffles. All the specimens taken at this time in these streams proved to be *Simulium vittatum*. A thorough search of the river margin at Peoria, made August 31, was without result, no trace of simulum being found in the main stream. Not a single winged black fly could be found here, although the presence of small numbers of the pupae showed that a very few might be abroad. The probability of any activity of black flies in conveying pellagra at this place and time seems, consequently, very small.

I have next to scan my miscellaneous data with reference to the possibility of distinguishing successive generations, and periods of greatest abundance of the insects on the wing. Throwing all these data together, I find that we have made collections of adults on thirty-six of the 204 days from April 3 to October 24, and that there are two rather conspicuous blanks in the series—one extending from May 22 to June 14, twenty-two days, and the other from July 21 to August 11, twenty days. Accepting these as indications of the dividing lines between successive generations, we may conclude provisionally that we have three generations

in the season, the first covering April and the greater part of May, the second the latter part of June and most of July, and the third extending from the middle of August to the last of October. These intervals might perhaps be filled in at least in part, if we had larger collections, but they correspond fairly well to such definite facts as we have concerning the length of a generation period of simuli. Precise work on this subject has been done only in New York, and there only for two species, *S. pictipes* and *S. venustum*, the first of which possibly does not occur in Illinois. For both these New York species it has been shown that in the warmer part of the summer the development of a generation requires about eight weeks—one of which is passed in the egg, four in the larva and three in the pupa stage. Making reasonable allowance for a prolongation of the period of development of the earliest and latest generations grown in the cooler weather of the season we may fairly suppose that we have three generations of six of our Illinois species, the first extending through April and May, the second coming in June and July and the third in August, September and October. Entomologists will readily understand that with any such succession of generations as this in a single season, the periods of the later ones are always the longer. The other three Illinois species seem to give us but one generation each which we know to appear in April and May.

It has been a matter of special interest to me to compare this hypothetical scheme of generations with pellagra data communicated to me by Dr. H. Douglas Singer in a letter written December 29, 1911. The statements of this letter are illustrated by a curve showing the number of fresh cases of pellagra occurring at the Bartonville General Hospital for each month from July, 1909, to September, 1911. There are five high points in this curve for these twenty-six months, one at the beginning of the record which, starting with twenty-one cases for July, 1909, rises to seventy-one for August, and then drops rapidly away to three in December. This is much the highest wave of the curve. The next wave of increase begins with a single case in April, 1910, rises to sixteen cases in May and to thirty-four in June, and drops to four in July. We have next a lower wave of sixteen cases in August, 1910, fifteen in September and one in October. Two cases in the following March (1911) become four in April and six in May, fall to one in June, rise again to three in July, and seven in August and fall to none in September.

On the supposition of a connection between black-fly outbreaks and pellagra waves we should naturally expect the former to precede the latter somewhat. Just how far, of course no one can tell, since that would involve a knowledge of the incubation period of the disease. A comparison of my hypothetical periods of our black-fly generations with these waves of frequency of new cases of pellagra gives an indication of a correspondence between the two series for the first two generations.

of the year, but negatives the idea of any stimulating influence of the implied third generation. Thus, omitting the 1909 record as begun too late to serve our purpose, the March and April generation of black flies for 1910 connects with an April and May increase of pellagra, the supposed June and July generation of that year with high numbers of new cases for August and September, the March and April generation of 1911 connects with an April and May increase of pellagra for that year, and the June and July generation with a July and August increase. The August to October generation, on the other hand, is followed by a decline in the number of new cases in both 1909 and 1910, the record for 1911 breaking off within this period.

These interpretations, it is true, are decidedly hypothetical, but they may be taken as at least suggestive of a causal relationship and as indicative of a method of analysis which, used in proper cases, may give definite results. We need to know accurately the life histories of the various species of simulium for the entire year in some locality where pellagra is more or less prevalent, and to know also the exact facts as to the local abundance of the winged flies during the successive generation periods. If there are recognizable and considerable variations in abundance, or definite breaks in the insect series, correlated in a uniform way with waves of pellagra increase presently following, and if exceptions to this correlation are to be clearly explained by exceptional circumstances, we shall have strong reason to believe that one or more of the species of simulium then and there present are causally related to the conveyance of pellagra from one person to another. Other and more direct lines of operation on this problem belong to the pathologist rather than to the entomologist.

#### IX. GENERAL SUMMARY AND DISCUSSION

1 *Pellagra in Illinois*—A conservative estimate of the number of pellagrins in this state from July, 1909, when it was first recognized to September, 1911, would be five hundred. The vast majority of these cases have occurred in the state and county hospitals for the insane, notably at the Peoria State Hospital. There has been a progressive diminution in the total numbers of new cases in the three years under consideration in these institutions. It is, however, becoming increasingly evident that there is a considerable number of cases outside the state hospitals, although we have no figures which will justify any statements as to the actual numbers. Two somewhat striking foci seem to exist in Chicago and Peoria but it is probable that the disease is prevalent over wide areas.

2 *Clinical Manifestations and Pathology*—Pellagra is a systemic disease characterized by a skin eruption, symptoms of gastro-intestinal disturbance and more or less well-marked general debility and emaciation. The only reliable diagnostic symptom is the skin eruption which begins



as a bright red erythema generally on the backs of the hands. This color becomes more copper-colored in the course of a few days with thickening of the epidermis, especially about the knuckles and often with fissures which bleed easily. In severe types bullæ form, which may rupture, and thus give rise to superficial ulcers. In the course of two or three weeks the color becomes gradually darker from increased pigment deposits and begins to desquamate. This stage lasts a variable time from a few weeks to several months, at the end of which the appearance is pink and delicate-looking, like that of an infant. Following this it gradually returns to a normal condition. The chief points in diagnosis are the course, the more or less absolute symmetry on the two sides of the body, the sharp line of demarcation from the healthy skin and the absence of marked itching and pain. The commonest sites are the backs of the hands and lower parts of the forearms, often extending as a cuff around the wrist just above the palm, the elbows and areas on the inner sides of the arms and forearms, the forehead and cheeks, the neck, and finally the dorsa of the feet. At times the eruption is widespread over the whole body. Denudation and swelling of the tongue with sometimes ulceration, inflammation and even ulceration of the mucosa of the cheeks, gums and lips should probably be regarded as manifestations similar to the skin eruption. Excoriations about the anus and genitalia, with inflammation of the mucosa of the vagina are fairly common.

The gastro-intestinal symptoms are very frequent, but not always marked and may be absent. They consist of diarrhea with liquid putrescent stools of peculiar odor, which is thought by some to be characteristic. More or less anorexia is present as a rule, but sometimes appetite is excessive.

Emaciation and general weakness are present in a degree more or less corresponding with the severity of the gastro-intestinal symptoms.

Besides these features there is a great tendency to the development of mental disorder of delirious type and in the late stages to the occurrence of the central neuritis syndrome.

The course of the disease is extremely variable. In many cases it consists of annual exacerbations lasting one or two months with apparent recovery in the intervals. Some patients seem to have one attack and then to recover, at any rate without recurrence during one pellagrous season. The percentage of recurrences in individuals recovering from an attack in 1909 was 31.25 in 1910 and 13.24 in 1911. Of the 1910 attacks which did not prove fatal only 8.6 per cent recurred in 1911.

*Death* may result in any attack whether the first or later recurrence. This may transpire during the acute phase apparently from general exhaustion, or at a later period, after all characteristic pellagrous lesions have disappeared, with symptoms of central neuritis. Pathologically one case dying during the acute stage presented lesions resembling those of

central neuritis, although the characteristic clinical syndrome was not observed during life. The mortality has been very high in this state, pellagra being given as the immediate cause of death in 49.6 per cent of the 258 cases at the Peoria State Hospital. Of the 408 cases recorded, 189, or 46.3 per cent, are dead, although in some of these instances intercurrent disease seemed to be the actual cause.

Symptoms which appear to be of bad *prognostic import* are the early appearance and severe degree of gastro-intestinal and mouth symptoms, marked emaciation and the occurrence of nervous symptoms such as delirium and signs of central neuritis.

*Treatment* has seemed to have but little if any influence on the course of the disease. Arsenic has been used in various forms, but the cases so treated do not seem to have shown any more favorable outcome than those without it. We can recommend only general measures such as careful nursing and diet, the avoidance of exposure to the sun, which seems to aggravate the skin lesions, together with the copious administration of fluids, which may if necessary be given by hypodermoclysis.

*Feces.* The stools of pellagrins are exceedingly variable in character. In general, there is a marked diarrhea during the acute attack, with frequent watery evacuations, nearly always very foul-smelling. Later, the stools become less fluid and contain abundant mucus. Blood and epithelial cells are frequently observed in severe cases.

The numerical relationships of the normal forms of fecal bacteria are more or less disturbed and new forms of bacteria of several different kinds appear in the feces in appreciable numbers. Protozoa, especially amebas and flagellates, are frequently found.

Cultures of the fecal bacteria in the various stages of pellagra also indicate disturbances of the normal relationships of the intestinal bacteria. In addition to this, some forms of bacteria not ordinarily found in the feces of healthy men are found here in appreciable numbers.

There is some evidence indicating that some of these bacterial and protozoal forms play a part in producing some of the pathological changes observed in the cases of pellagra which we have studied. Whether any of them is a primary factor in the disease itself, or whether they are all secondary invaders with no essential causal relation to pellagra, cannot be decided from the evidence at hand. For those forms which have been studied more particularly by us the latter hypothesis seems to be the more probable. Nevertheless, these bacteria and protozoa seem to be worthy of further attention.

*Blood.* Moderate anemia is the rule with a color index which is frequently normal or even slightly above. Leukocytosis occurs occasionally in severe cases, but as a rule the number of white cells is within normal limits. There appears to be no characteristic change in the relative proportions of the different varieties of white cell.

No abnormalities are noticeable in the size, shape and staining properties of the red cells. No abnormal bodies have been found either in fresh or in stained specimens. Cultures have been almost all sterile.

**Urine.** Indican has been increased and there are variations in color, quantity, specific gravity and composition. A trace of albumin with hyaline casts are not uncommon.

**Cerebrospinal fluid.** This shows no increase of cell elements or albumin content and cultures have been uniformly sterile.

**Complement fixation tests** with the blood-serum of pellagrins as an amboceptor and extracts of pellagious liver, tongue and spleen as antigen have given results which cannot be regarded as specific at present. Negatives with positive cases and positives with normal sera have been encountered too frequently to permit of any interpretation.

**Anaphylactic tests** by von Piquet's method using extracts of healthy and damaged maize have proved uniformly negative.

The post-mortem findings are those of a generalized intoxication. Fatty degeneration of the liver with inflammation and ulceration of the intestinal mucosa and the occurrence of islets of subacute inflammatory exudate in the portal canals of the liver suggest an intoxication of intestinal origin which may be either primary or secondary. There is nothing characteristic of pellagra in the lesions found in the nervous system, they can only be regarded as evidence of an intoxication.

The chemical analysis of one pellagious brain shows no deficiency in sulphur or phosphorus, but only a disturbance in the combinations of the former. This is quoted here only in relation to the possibility of a deficiency in certain elements in the diet which has been suggested as a cause for pellagra.

**3 Animal Experimentation.** Inoculations of monkeys and other animals with tissue emulsions and body fluids have been entirely unsuccessful.

Feeding with the dejecta of human pellagrins has given rise to no symptoms. Similar negative results were obtained from inoculation with organisms isolated from the stools.

Feeding experiments with maize both healthy and in a spoiled condition have been without result.

Injection of extracts from maize contaminated with five different molds was found to be toxic in one instance only, the organism being *Monascus purpureus*. Another sample containing a blue-green *Penicillium* and contaminated with bacteria was highly toxic.

**4 Diet.** Maize has formed but a small part of the hospital dietaries and the quality used has been excellent. Careful observations of a squad of individuals fed with a large excess of corn products for a period of

twelve months compared with a similar number given a strictly corn-free diet revealed no differences in the number of cases or the severity of pellagra which developed in both

Detailed study of the general diet of the Peoria State Hospital reveals a deficiency in protein constituents and especially in animal protein. Comparisons between the average amount of meat supplied to the inmates of the Peoria and other state hospitals suggest a greater or less degree of deficiency in animal protein in all. It is also noticeable, although it may be quite accidental, that pellagra has diminished in Peoria and Dunning, coincidently with an increase in meat supply, while at Elgin the number of pellagrins has increased with a decrease in the amount of meat provided *per capita*.

#### GENERAL DISCUSSION OF THEORIES AS TO ETIOLOGY

The various conceptions as to the etiology of pellagra have already been enumerated under the head of "Current Views on Pellagra," as the basis on which the work of this commission was planned. It is therefore only necessary here to discuss the bearing of the work accomplished on these different theories. This can with advantage be arranged under the same two main headings:

1 *In Relation to Maize*—It may be said that all work directed to this question has uniformly yielded negative results. The evidence collected in this report all tends to discredit any such assumption, and while we fully appreciate that negative findings can never be accepted as positive proof for or against any given proposition, it nevertheless seems to us that the burden of proof must rest with the zeists. The following facts may be especially emphasized as tending to discredit any causal relations between maize and pellagra: (1) *Sound maize* (a) Excessive corn feeding was not accompanied by more pellagra than was observed in individuals kept on a strictly corn-free diet, other conditions being as far as possible, identical as regards the age, sex, mental and bodily condition, habits and occupation of the patients and the size, location and general arrangement of the buildings, although cases developed under both conditions, (b) maize products constituted only a moderate proportion of the general diet of those affected, (c) cutaneous tests in pellagrins with extracts of corn gave rise to no anaphylactic symptoms. (2) *Damaged maize* (a) The corn used in the state institutions has been of high grade, (b) all experimental work has necessarily been performed on animals. In none has there been any pellagra-like manifestations, and, in fact, with few exceptions the toxicity has been low, (c) cutaneous anaphylaxis tests with extracts from damaged corn were negative.

If one adds to these direct observations the keen critical analysis by Sambon of the foundations on which the maize hypothesis rests, one cannot but feel that the arguments in its favor are extremely slender.

2 *Antizest Theories*—As long ago as 1905 Sambon<sup>8</sup> discussed the probability that pellagra was an infective disease, the causative agent of which was carried by some blood-sucking insect. His reasoning is based on analogies with other infections of that character. The main grounds are, (1) the seasonal recurrence, (2) the existence of endemic foci, while, apparently the disease is not contagious, (3) the fact that recurrences occur in previously infected individuals even after they have been removed from the infected locality and such recurrences occur at the same seasons of the year.

All investigations carried out by us with the object of demonstrating the presence of a blood parasite have so far failed. Nevertheless, it is quite possible that a parasite may live and propagate in the blood, but require special methods for its demonstration not yet discovered. The failure to produce pellagra in animals with such infected blood may well be the consequence of various reasons. For instance, it is quite possible that, as Sambon supposes, some second phase of existence in an intermediate host such as the biting insect, may be necessary. Again the animals used for experimentation may not be susceptible. It is thus quite obvious that the negative findings so far enumerated cannot be accepted as entirely controverting this theory.

Post-mortem findings do suggest a possible nidus for the growth of an organism in the intestine, a suggestion which might be considered as especially plausible from the clinical picture. Nevertheless, it must always be remembered that the infection of the intestinal tract may be secondary to, and not causative of, pellagra. We have studied the fecal flora with especial care and do not consider that our findings justify us in making any claim for them as primary causal factors.

The relation of simulia to pellagra, hypothecated by Sambon, finds but little support from the researches we have been able to make. The particular variety *S. reptans*, which he claims to be of world-wide distribution, is said by Professor Forbes to be unknown in North America as yet except in Greenland.

Quite recently, and therefore not included in the statistical studies, we have had the opportunity to observe two cases, both apparently first attacks, in which pellagra developed during the winter months following several weeks of intensely cold weather. One of these arose at the Kankakee State Hospital, the first symptoms being observed Dec. 24, 1911. This patient had been an inmate of the hospital more than a year and had shown no previous signs of pellagra. The attack was very severe and ended fatally. The second case developed Dec. 31, 1911, at the Jacksonville State Hospital. This man had also been in the hospital for over a year. Professor Forbes informs us that the latest date on which adult simulia have been captured in Illinois is Oct. 24. It would there-

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<sup>8</sup> Brit. Med. Jour., 1905, ii, 1272.

fore be necessary to concede an extremely long incubation period in order to explain these cases on the theory that the *causa morbi* is borne by these insects

#### PREVENTION

This discussion would not be complete without consideration of the problem of prevention. The evidence seems conclusive that poor nutrition is an important factor in predisposing to the disease, although we fully admit and can confirm the occurrence of pellagra in persons well nourished and apparently robust. The investigation of the dietaries of the state institutions reveals no defect in quality or quantity. There does, however, seem to be a low animal protein content. The Italian peasantry have suffered more from pellagra than any other people, and their diet consists almost exclusively of maize in the form of polenta. They eat practically no meat, fish, milk or eggs. In fact, it may be said that meat becomes a luxury in all conditions of poverty. Maize has a large protein value, but this, apparently, cannot satisfactorily take the place of animal protein altogether. It may be then, that conditions in which the animal protein content of the diet is low, constitute a predisposing factor to infection with pellagra. In making this suggestion, we emphatically do not wish to be misunderstood. The dietaries of the state hospitals in Illinois are fully up to the usual standards in such institutions elsewhere and we do not consider that pellagra is due to lack of food or even to deficiency in any particular constituent of the food. Our impression is rather that pellagra is due to infection of the body with some micro-organism. It does seem possible, however, that a diet deficient in animal protein may so alter the body that the infecting organism has a better chance to grow.

#### CONCLUSIONS

In closing this report we feel that certain conclusions are advisable for the purpose of representing our views on the lines which should be followed in further studying and dealing with this problem. They are purposely expressed in somewhat general terms.

- 1 Pellagra is a disease due to infection with some living micro-organism

- 2 A possible habitat for this parasite in man is the intestinal canal

- 3 Deficient animal protein in the diet may constitute a predisposing factor in the contraction of the disease

- 4 The number of cases of known pellagra renders this disease a decided menace to the public health of this state

- 5 Careful search for, and investigation of, suspected cases outside the state hospitals for the insane is extremely desirable in view of experience elsewhere

# THE EFFECT OF THE TUBERCULO-TOXIN ON THE ADRENAL FUNCTION

L H NEWBURGH, BOSTON AND T H KELLY, CINCINNATI

The following work was undertaken for the purpose of producing an experimental chronic insufficiency of the adrenal glands. It was then our intention to study this experimental insufficiency in relation to the other glands of internal secretion, and to compare it with the clinical picture of Addison's disease.

Thus far all experimental work has resulted only in an acute insufficiency of the adrenal function. Excision of the glands is followed by death in two or three days. It was accordingly necessary to devise some means of slowly but progressively injuring the function of the glands. For this purpose it was decided to try the injection of tuberculin over long periods. Tuberculin was selected because of the evidence presented by certain workers in this field that chronic tuberculosis causes a sclerosis and atrophy of the adrenal glands.

Bernard and Bigard<sup>1</sup> have found, in the adrenals of the tuberculous, a sclerosis beginning at the vessels, causing lobulation of the glands, especially manifest in the cortex, but also invading the medulla. This can go on to complete atrophy in cases of intense sclerosis. Parisot and Lucien<sup>2</sup> have shown that the extracts of the adrenals of persons dying of chronic tuberculosis have a less intense hypertensive action than those of normal extracts. Boinet<sup>3</sup> states that cases of adrenal sclerosis are more numerous than primary tuberculosis or cancer of the adrenals, and that this condition, with or without *melanoderme* is common in the course of, or at the end of, pulmonary tuberculosis. The above mentioned workers believe that the anatomical and physiological changes noted by them resulted from the action of the tuberculo-toxin.

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\*From the Joseph Eichberg Laboratory of Physiology, University of Cincinnati.

1 Bernard, L, and Bigard. Les processus sécrétoires dans la substance corticale de la glande surrénale. *Compt rend Soc de biol*, 1905, lxx 504 (quoted by Boinet)

2 Parisot, J, and Lucien, M. Etude physiologique et anatomique des capsules surrénale chez les tuberculeux. *Reunion biologique de Nancy*, 1907, lxii, 525 (quoted by Boinet)

3 Boinet, E. Opothérapie Surrénale dans la maladie d'Addison. *Bull de l'Acad de Méd, Paris*, 1909, series 3, lxxi 154

It seemed reasonable to assume that Koch's old tuberculin<sup>4</sup> contained these toxins, and that if the changes described by Bernard and Bigard, Parisot and Lucien, and Boinet, were caused by products resulting from the growth of the tubercle bacillus in the human body, we might expect to produce similar effects by injecting tuberculin into rabbits. It was thought better to use tuberculin<sup>5</sup> rather than to inoculate the animals with living bacilli because in the former case we could regulate the dose and because we could be sure there were no tubercle bacilli in the adrenal glands.

Our experimental procedure was as follows. We employed two series of animals. In the first series we started with very small doses of tuberculin in order not to kill the rabbits should they develop the signs of a toxemia. The first injections were 0.01 gm repeated daily. No evidence of disease being noted, we gradually increased the dose up to 0.10 gm. In the second series the dose throughout was 0.10 gm. In no case did the animals show any of the symptoms of a toxemia. They did not lose weight or strength, remained lively and ate well. In several instances they gained weight.

The two functions of the adrenal secretion which are most firmly established, are the glycogenic and the pressor. It has been shown by Porges<sup>6</sup> and others that persons suffering from Addison's disease, and dogs from whom the adrenals have been excised, have an amount of glucose in the blood far below the normal. Subcutaneous injections of adrenalin, on the other hand, cause a transient hyperglycemia. A low blood-pressure occurs in the great majority, and perhaps in all cases of true Addison's disease. Injections of minute doses of adrenalin, on the other hand, cause a sharp rise in blood-pressure.

In order to find whether we had interfered with or destroyed the functions of the adrenal glands in our animals we in the first place compared the percentage of glucose present in the arterial blood of rabbits which

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<sup>4</sup> Koch's old tuberculin (H. K. Mulford & Co.) is prepared as follows: Tubercle bacilli are grown on glycerated broth for from thirty to sixty days. The culture is then poured into flat dishes and evaporated to one-tenth its original bulk over live steam. The filtrate from this concentrated broth is the finished product.

<sup>5</sup> Concentrated old tuberculin was mixed with a sufficient amount of 0.9 per cent salt solution to give the desired dilution. One c.c. of this solution was received into each of a series of ampoules, the latter were sealed and submerged in water, the water was boiled for five minutes. It was found necessary in the absence of a preserving fluid to take these precautions in order to maintain sterility.

<sup>6</sup> Porges, O. Zur Pathologie des Morbus Addison. Ztschr. f. klin. Med., Berl., 1910, LXX, 243.



had received injections of tuberculin over a long period of time with that found in normal rabbits <sup>7</sup>

A striking decrease in the glucose content of the blood was found. In Rabbit XXIII, after 4.55 gm of tuberculin had been given in the course of four months, and in Rabbit XXXV, after 7.1 gm had been given in the course of three months, the glucose was present in such minute amounts that no test with Fehling's solution could be obtained. It is interesting to note that, in these same rabbits, there was no definite hypoglycemia after Rabbit XXIII had received 0.81 tuberculin in the course of three months, and after Rabbit XXXV had received 3.1 tuberculin in the course of one month and a half. In another rabbit, No. XXV, after 4.31 gm tuberculin had been given in the course of four months, an infinitesimal amount of glucose—0.006 per cent—was found. This rabbit after receiving 0.87 gm of tuberculin in the course of two months, showed a blood sugar content which equaled about 50 per cent of the normal. Rabbit XXXIV, after 7.7 gm of tuberculin in the course of three months showed less than half of its normal percentage of glucose. It would seem that the total length of treatment was a more important factor in determining the decrease in the blood sugar content than the total amount of tuberculin injected. The accompanying table shows clearly the effect of tuberculin on the per cent of glucose in the blood.

In the next place we employed a method described by Cooke<sup>8</sup> to find whether we had interfered with the pressor function of the adrenal glands in our experimental animals. Cooke wished to compare the pressor effect of the adrenals of a person dying of tuberculosis of the

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<sup>7</sup> The method used for determining the percentage of glucose in the blood was as follows. After fasting twenty four hours, the rabbit was etherized, the carotid artery dissected free and bled into a 50 cc volumetric flask containing 5 cc of a 2 per cent ammonium oxalate solution, until the flask was about three fourths full. Distilled water was then run into the flask from a buret up to the 50 cc mark, the amount of water used, noted, and this plus 5 subtracted from 50 to determine the amount of blood obtained. To 200 cc of a 2 per cent solution of HCl and 200 cc of a 5 per cent solution of HgCl<sub>2</sub>, contained in a 500 cc graduate, the contents of the flask, and enough water to make 500 cc were added and the whole filtered. H<sub>2</sub>S was passed through the filtrate until a black precipitate was obtained and this was then filtered and the amount of filtrate noted. From this the proportion of the original 500 cc remaining as filtrate, and so the proportion of the blood it contained, was calculated. The filtrate was neutralized with NaOH and evaporated to about 25 cc. Fehling's solution was added in excess. The resulting precipitate was collected on an ash free filter paper, washed until no reaction for sulphates was obtained, dried, ignited in a weighed porcelain crucible and weighed. This gives the weight of the CuO thrown down by the glucose. From this the amount of glucose in the original volume of blood, and so the percentage, is calculated.

<sup>8</sup> Cooke, J. V. Some Observations on the Blood Pressure Raising Substance of the Adrenals in Acute Adrenal Insufficiency. *THE ARCHIVES INT MED*, 1912, 14, 108.

adrenals, with that found in human beings dying of some other disease. He found that the diseased portions of the tuberculous adrenals caused no rise in the blood-pressure tracing of a dog, whereas, the extract of the "normal" adrenals caused a rise quite similar to that produced by injection of adrenalin. A "normal" rabbit was etherized, the carotid artery exposed and connected with a writing lever through a mercury manometer. The rabbit's normal pressure was written on a kymograph. One of the "treated" animals was killed, the adrenal glands removed, ground in a mortar with sand and ten volumes of salt solution added and centrifugalized. A portion of the supernatant fluid was injected into the ear vein of the "normal" rabbit. It will be seen (Figures 1 and 2), that a sharp marked rise occurred very quickly. We must conclude from these tracings that the pressor function of the adrenal secretion had either been interfered with very slightly or not at all.



Fig 1—Effect on blood pressure of experimental injection of extract of adrenal gland in a rabbit. A Intravenous injection of 2 ccm of the extract of the adrenal glands of Rabbit No XXXV. B Intravenous injection of 2 ccm of normal salt solution. C Intravenous injection of 1 minim of adrenalin (P. D. & Co.). The marked pressor effect of the adrenal extract is apparent. This animal's blood contained so little glucose that no precipitate with Fehling's solution could be obtained.

If we now try to interpret our findings, we would say that the marked hypoglycemia produced would strongly suggest that an extreme degree of functional insufficiency of the adrenal secretion had been brought about. On the other hand, such a conclusion is not warranted in the face of the fact that the pressor function remains intact and that none of the Addisonian symptoms were noted. Most of the data at our disposal lead us to believe that the glycogenic and pressor functions go hand in hand—that no marked alteration occurs in the one without affecting the other. In Addison's disease we find not only a hypoglycemia but also a low blood-pressure. After injection of adrenalin we get not only a hyperglycemia but also an increased blood-pressure.

The evidence which might be presented to show that changes can occur in the glycogenic function without involving the pressor function

TABLE SHOWING EFFECTS OF TUBERCULIN ON THE ADRENAL FUNCTION

Experiment No	Per Cent Glucose in Blood Before Treatment	Per Cent of Glucose in the Blood after a Certain Number of Injections	Per Cent of Glucose in the Blood after Total Number of Injections	Weight Before Treatment Kilos	Weight at End of Experiment, Kilos	Remarks
XXIII		Fifteen injections of tuberculin 0.01 gm each, $\pm$ 9 injections of tuberculin 0.02 gm each, + 8 injections of tuberculin 0.06 gm each 0 130	Fifteen injections of tuberculin 0.01 gm each + 9 injections of tuberculin 0.02 gm each + 12 injections of tuberculin 0.06 gm each, + 35 injections tuberculin 0.10 gm each 0 0	1.9	1.9	The animal throughout the experiment was strong and active, and showed no evidence of disease
XXIV XXV	0 150	Nine injections of tuberculin, 0.01 gm each, + 9 injections of tuberculin 0.02 gm each, + 10 injections of tuberculin 0.06 gm each 0 082	Nine injections of tuberculin, 0.01 gm each + 9 injections of tuberculin 0.02 gm each, + 14 injections of tuberculin, 0.06 gm each, + 32 injections of tuberculin 0.10 gm each 0 006	2.0 1.9	2.2	Normal control The animal throughout the experiment was strong and active and showed no evidence of disease <i>Thirty five days after the last injection of tuberculin the per cent of glucose in the blood was found to be 0.09% It had returned to about the normal area</i>
XXX XXXIV	0 098 0 133		Seventy seven injections of tuberculin 0.10 gm each 0 061	2.0 2.7	2.7	Normal control The animal throughout the experiment was strong and active and showed no evidence of disease
XXXV		Glucose still present in marked amount after 31 injections of tuberculin 0.10 gm Precipitate of CuO lost	Seventy one injections of tuberculin 0.10 gm each 0 0	2.0	1.9	The animal throughout the experiment was strong and active and showed no evidence of disease January 24 1912 a litter of four born dead
Averages	0 127		0 016			

and *vice versa*, is not of a very convincing nature. Shui and Wiesel,<sup>9</sup> Goldzieher and Molnár,<sup>10</sup> and Goldzieher<sup>11</sup> have tried to prove that the blood of chronic nephritics contains an excess of adrenalin, and they have attributed the high blood-pressure found in this disease to the action of this excess. If this were a fact we should have an example of a pressor effect without a corresponding glycogenic one. But O'Connor<sup>12</sup>, Broking and Tiendelenburg,<sup>13</sup> and Falta and Flemming<sup>14</sup> have shown that the methods used for determining the amount of adrenal secretion present in the blood serum, are faulty, and that consequently, the conclusions based on these methods are not tenable. Falta<sup>15</sup> has suggested that human diabetes mellitus might, in certain instances, be the result of overfunction of the adrenal glands. If such were the case this would serve as an example of a glycogenic effect without a corresponding pressor effect. But we have no direct evidence in support of Falta's hypothesis.

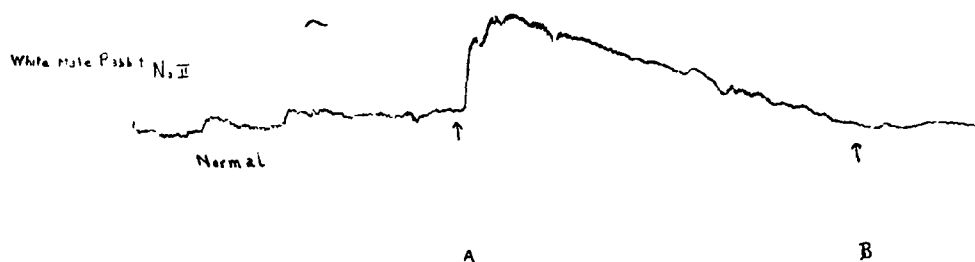


Fig 2—Effect on blood pressure of experimental injection of extract of adrenal gland in a rabbit. A Intravenous injection of 0.8 ccm. of the extract of the adrenal glands of Rabbit No. XXXIV. B Intravenous injection of 1.6 ccm. of normal salt solution. The marked pressor effect of the adrenal extract is apparent. This animal's blood showed a more than 50 per cent reduction in the glucose content.

<sup>9</sup> Shui H., and Wiesel J. Beiträge zur Physiologie und Pathologie des chromaffinen Gewebes. Wien klin. Wchnsch., 1907, **xx**, 1202.

<sup>10</sup> Goldzieher M. and Molnár, B. Beiträge zur Frage der Adrenalinamie, Wien klin. Wchnsch., 1908, **xxi**, 215.

<sup>11</sup> Goldzieher M. Beiträge zur Pathologie der Nebennieren. Wien klin. Wchnsch., 1910, **xxiii**, 869.

<sup>12</sup> O'Connor, J. M. Ueber Adrenalinbestimmung im Blute. München med. Wchnsch., 1911, **lviii**, 1439.

<sup>13</sup> Broking E. and Tiendelenburg P. Adrenalin-nachweis und Adrenalin-gehalt des menschlichen Blutes. Deutsch. Arch. f. klin. Med., 1911, **cxviii**, 168.

<sup>14</sup> Falta W. and Flemming G. B. Ueber die Wirkung des Adrenalins und Pituitins auf den überlebenden Kaninchenuterus und über die Verwertbarkeit der Uterusmethode für den Adrenalin-nachweis im Serum. München med. Wchnsch., 1911, **lviii**, 2649.

<sup>15</sup> Falta W. Ueber die Gesetze der Zucker- Ausscheidung beim Diabetes mellitus. Ztschr. f. klin. Med. Beil., 1908, **lxv**, 300.

<sup>16</sup> Fischer Martin H. Personal communication.

Martin H. Fischer<sup>16</sup> has suggested that our findings might be explained on the basis of fever produced by the tuberculo-toxin which so increased the carbohydrate metabolism of the rabbit that there was produced within the organism a great reduction of the glycogen content. This explanation might be possible but it seems to us that such marked reduction in the amount of glycogen as would be required to produce such results as were obtained in Rabbits XXIII, XXV and XXXV must necessarily be accompanied by some of the symptoms of infection such as loss of appetite, loss of weight, languor and weakness, none of which occurred as may be seen by consulting the table. Rabbit XXXV lost 0.1 kilos but this is explained by the fact that it was weighed for the first time very near the end of pregnancy. Rabbits XXIII and XXXIV maintained a constant weight and Rabbit XXV gained 0.3 kilos. At no time during the course of our experiments did any of these rabbits show any sign or symptom of disease.

It is impossible in the present state of our knowledge to give a satisfactory explanation for the results we have obtained.

#### PROTOCOLS

PROTOCOL 23—Belgian hare. Male 1.9 kilos. From June 11, 1911, to July 9, 1911, fifteen subcutaneous injections of tuberculin 0.01 gm. at each injection.

From July 11, 1911, to July 27, 1911, nine injections of tuberculin 0.02 gm. at each injection.

From July 28, 1911, to August 29, 1911, twelve injections of tuberculin 0.06 gm. at each injection.

From August 30, 1911, to the end of the experiment November 5, 1911, thirty-five injections of tuberculin 0.10 gm. at each injection.

August 13, 1911, blood from right carotid artery showed 0.130 per cent glucose.

October 22, 1911, blood from left carotid artery showed *no precipitate with Fehling's solution*.

PROTOCOL 24—Black and white rabbit. Male 2.6 kilos.

June 14, 1911, blood from right carotid artery showed 0.150 per cent glucose. No further observation.

PROTOCOL 25—White rabbit. Male 1.9 kilos.

From June 23, 1911, to July 9, 1911, nine injections of tuberculin, 0.01 gm. at each injection.

From July 11, 1911, to July 27, 1911, nine injections of tuberculin 0.02 gm. at each injection.

From July 30, 1911, to August 29, 1911, fourteen injections of tuberculin 0.06 gm. at each injection.

August 19, 1911, blood from right carotid artery shows 0.082 per cent glucose.

From September 2, 1911, to November 5, 1911, thirty-nine injections of tuberculin 0.10 gm. at each injection.

October 29, 1911, blood from left carotid artery shows 0.006 per cent glucose.

December 10, 1911, thirty-five days after the last injections of tuberculin, blood from femoral artery shows 0.094 per cent glucose.

PROTOCOL 30—White rabbit. Female 2.0 kilos.

Blood from right carotid artery shows 0.098 per cent glucose. No further observation.

PROTOCOL 34—White rabbit. Male, 2.7 kilos.

December 23, 1911, blood from right carotid artery shows 0.133 per cent glucose.

December 28, 1911, to April 14, 1912, ninety injections of tuberculin, 0.10 gm at each injection

April 1, 1912, blood from left carotid artery shows 0.061 per cent glucose

April 15, 1912, animal killed by a blow on the head. Adrenal glands removed and macerated in salt solution, 2 c.c. injected into the ear vein of a normal rabbit writing blood pressure as shown in Fig. 2

PROTOCOL 35—Black and white rabbit. Female, 2.0 kilos. January 8, 1912 to April 6, 1912, seventy-five injections of tuberculin, 0.10 gm at each injection. January 24, 1912, a litter of four born dead.

February 16, 1912, blood from right carotid artery shows a definite glycemia. Precipitate lost.

April 2, 1912, blood from left carotid artery shows *no precipitate with Fehling's solution*.

April 7, 1912, animal killed by a blow on the head. Adrenal glands removed and macerated in salt solution. Two c.c. injected into the ear vein of a normal rabbit writing blood pressure as shown in Fig. 1.

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# STUDIES IN AUSCULTATORY BLOOD-PRESSURE PHENOMENA

## I THE EXPERIMENTAL DETERMINATION OF DIASTOLIC PRESSURE

LOUIS M WARFIELD M D  
MILWAUKEE WIS

### INTRODUCTION

The increasing conception of the importance of blood-pressure determinations as aids in medical diagnosis has led to considerable work on this subject

Since Korotkoff,<sup>1</sup> in 1905 demonstrated his auscultatory phenomenon there has been a gradual adoption of this method following the recommendations of workers who have made comparative readings with this and Uskov's sphygmomanometer von Recklinghausen's tonometer and Pals sphygmoscope As there seemed still to be a difference of opinion regarding the point where the diastolic pressure should be read the majority of German authors holding that it should be read at the so-called fourth phase where the loud sound suddenly becomes dull the Americans using the disappearance of all sound the fifth phase as diastolic pressure reading an attempt was made to settle the question by actually recording pressure and sounds simultaneously on dogs

### THE DIASTOLIC PRESSURE AND ITS DETERMINATION

Howell and Brush<sup>2</sup> were the first to show experimentally that the maximum oscillations of a lever attached to a mercury column corresponded to the diastolic pressure This was further delimited by Erlanger and Hooker,<sup>3</sup> who working with normal men with the former's instrument, showed that the point where diastolic pressure should be read was at the sudden diminution of the size of the maximum oscillations In an elaborate critical review of the literature bearing on blood-pressure and particularly diastolic and pulse-pressure, with the relation of the pulse-pressure to the velocity of blood-flow they concluded that there was some relationship between the velocity of blood and the pulse-pressure which

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\*From the Physiologic Laboratory of the University of Wisconsin Prof J A F Exster, Director

1 Korotkoff Zur Methodik der Blutdruckmessung Mitt d k mil med Akad zu St Petersburg 1905 vi 365

2 Howell and Brush A Critical Note upon Clinical Methods of Measuring Blood Pressure Boston Med and Surg Jour, 1901 cxlv 146

3 Erlanger and Hooker An Experimental Study of Blood Pressure and of Pulse Pressure in Man, Johns Hopkins Hosp Rep 1904, vi 145

could be expressed as velocity = pulse-rate  $\times$  pulse-pressure. They however, were careful to call attention to several modifying factors, but on the whole they thought that given certain constant factors all of which would hardly change at one time, the relationship between pulse-pressure and velocity held good. Dawson and Gorham,<sup>4</sup> in an experimental study of the relationship of pulse-pressure to systolic output, conclude that "under normal conditions and during various procedures (namely, stimulation of the vagus centrally and peripherally, saphenus nerve centrally, and of the annulus aëusentis, intravenous transfusion of 0.7 per cent sodium chlorid solution, intra-arterial transfusion of strong carbonate, bleeding and asphyxia) the pulse-pressure is a reliable index of the systolic output."



Fig 1—All figures are to be read from left to right. The top line records the points where sounds were heard, the figures above the short vertical lines refer to tones (see text). M B P maximum blood pressure. M B P minimum blood pressure. P B pressure bulb recorder. It was impossible to lower and raise this bulb by hand without obtaining the great irregular oscillations of the attached lever above the mercury manometer. B L base line.

There have been described four methods of estimating the diastolic pressure: 1 The oscillatory (Janeway, Masing); 2 The palpatory (Strasburger, Hirschfelder); 3 The graphic (v. Recklinghausen, Erlanger); 4 The auscultatory (Korotkoff).

Korotkoff in his original communication called attention to the fact that the diastolic occurred at the end tone, that is, at the point where the clear third tone was suddenly replaced by a dull tone. His reasons were theoretical.

<sup>4</sup> Dawson and Gorham. The Pulse Pressure as an Index of Systolic Output, Jour. Exper. Med. 1908, 1: 484.



Fischer<sup>5</sup> found the oscillatory maximum and minimum and compared them with the auscultatory maximum and minimum. He used the v Recklinghausen instrument. He found that in 150 cases the oscillatory and auscultatory minimum were equal in forty-seven cases. In fifty-five the oscillatory was practically equal to the auscultatory, 1 to 3 mm Hg less negligible values. In twenty-four the difference was 4 to 6 mm, in twelve cases 12 to 16 mm. In 102 cases with the v Recklinghausen instrument therefore there was agreement between oscillatory and auscultatory minimum. Fischer arrived at the conclusions that the auscultatory method of measuring blood-pressure was the most accurate and that the diastolic reading occurred at the so-called fourth phase i. e. when the loud tone of the third phase suddenly becomes dulled.



Fig 2—Tracing of auscultatory phenomena. See explanation in legend of Figure 1.

Lang and Manswetona<sup>6</sup> compared the auscultatory method of Korotkoff with the graphic method on the v Recklinghausen tonometer. They found that the onset of the third tone was coincident with the greatest oscillation of the tonometer. They stated that the auscultatory method could not be applied to dogs. It is not clear in their description just what method they used in their work on dogs. They speak of a physiological

5 Fischer J. Die Auskultatorische Blutdruckmessung im Vergleich mit der oszillatorischen von Heinrich von Recklinghausen und ihr durch die Phasenbestimmung bedingte Wert, *Ztschr f diät u physik Therap* 1909 vii, 389.

6 Lang and Manswetona. Zur Methodik der Blutdruckmessung nach v Recklinghausen und Korotkoff. *Deutsch Arch f klin Med* 1908, xciv, 441.

and clinical method and say that they had success in dogs only with the oscillatory method. From their experiments they concluded that the diastolic pressure was coincident with the change from the greatest oscillation to one definitely smaller.

The diastolic pressure is not, according to them, to be taken when the oscillations are largest, but at the place where the greatest oscillations become suddenly smaller or where the ordinary loud tone gives place to a dull tone, viz., at the so-called fourth phase (Ettinger<sup>7</sup>).

At the moment when one notes the first decrease in size of the greatest oscillations, the Korotkoff tone becomes suddenly weaker, then soon ceases or suddenly the tone vanishes entirely. This first decrease in size of the largest oscillations and the first dulling of Korotkoff's end tone marks the diastolic pressure and not the end of the large oscillations and the complete disappearance of all sound phases.

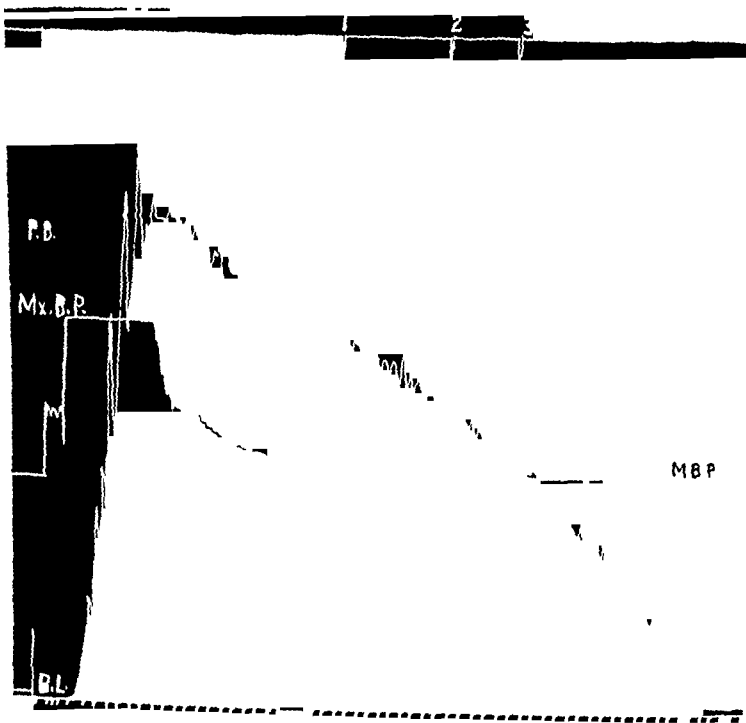


Fig. 3—Tracing of auscultatory phenomena. See explanation in legend of Figure 1.

Ettinger<sup>8</sup> demonstrated with his instrument that by the method of continuous escapement the diastolic pressure was at a point where the maximum oscillations suddenly became smaller. His readings were within 5 mm. of the actual diastolic pressure. By means of the intermittent escapement he obtained records showing this same point. He made an artificial encirculation schema using among other materials a piece of

<sup>7</sup> Ettinger. Die auscultatorische Blutdruckmessung nach Korotkoff. Wien klin. Wchnsch. 1907, 88, 992.

<sup>8</sup> Ettinger, J. A New Instrument for Determining the Minimum and Maximum Blood Pressures in Man. Johns Hopkins Hosp. Rep. 1904, 11, 53.

recently removed artery which was placed in a plethysmograph and connected with a manometer and with a pressure bottle. He proved that the diastolic pressure was coincident with the greatest expansion of the artery and he noticed that when the artery was expanding to its fullest extent at every pulsation there was a clicking tone produced. Van Westenhuyk<sup>9</sup> made comparative readings with the auscultatory method and the Uskov's sphygmomanometer and with Pal's sphygmoscope. He considered that his experiments showed that the greatest excursions of the lever of Uskov's instrument and the greatest oscillations of Pal's instrument were coincident with the second clear tone heard with the stethoscope (the third phase). He found that the sudden fall in maximum excursions was very near or at the disappearance of all tone in the majority of cases studied.

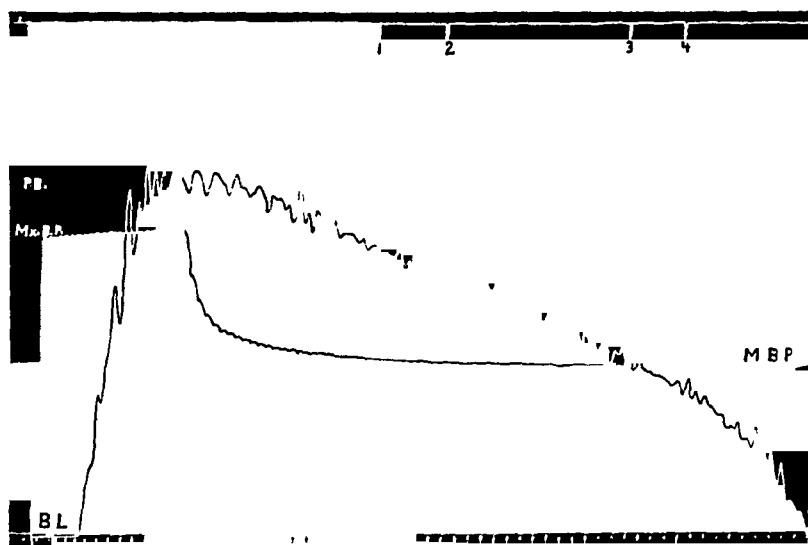


Fig 4.—Tracing of auscultatory phenomena. See explanation in legend of Figure 1.

Hirschfelder<sup>10</sup> mentions some determinations made at the Johns Hopkins Hospital with the Erlanger instrument and the auscultatory method which seemed to show that the disappearance of all sound the fifth phase, was the point where diastolic pressure should be read.

Articles in American literature (Gittings<sup>11</sup> Goodman and Howell<sup>12</sup>) have considered the disappearance of all sound as the diastolic pressure,

9 Van Westenhuyk N. Ueber die Beziehungen der Tonmethode der Bestimmung des Maximal und Minimal Blutdrucks zu den übrigen Methoden und über die Bedeutung dieser Grössen, *Ztschr f klin Med*, 1908, LXXI, 465.

10 Hirschfelder, A. D. *Diseases of the Heart*, etc.

11 Gittings J. C. The Auscultatory Blood Pressure Phenomenon, *THE ARCHIVES INT MED* 1910, VI, 196.

12 Goodman and Howell. The Auscultatory Blood Pressure Phenomenon, *Univ Penna Med Bull* 1910 XLIII 469.

and have seemingly ignored the most important of the German articles, taking Ettinger's word that the disappearance of all sound was the point where the diastolic pressure should be measured

#### EXPERIMENTAL DATA

The problem was Is it possible to use the auscultatory method to prove experimentally that a certain change of tone and not the disappearance of all sound, indicates the point to read diastolic pressure?

*Method and Apparatus*—Dogs were etherized and a tracheal cannula placed in the trachea connected with the usual ether bottle. It was aimed to produce uniform narcosis throughout a series of observations on a dog. The right femoral artery was connected with a mercury manometer the

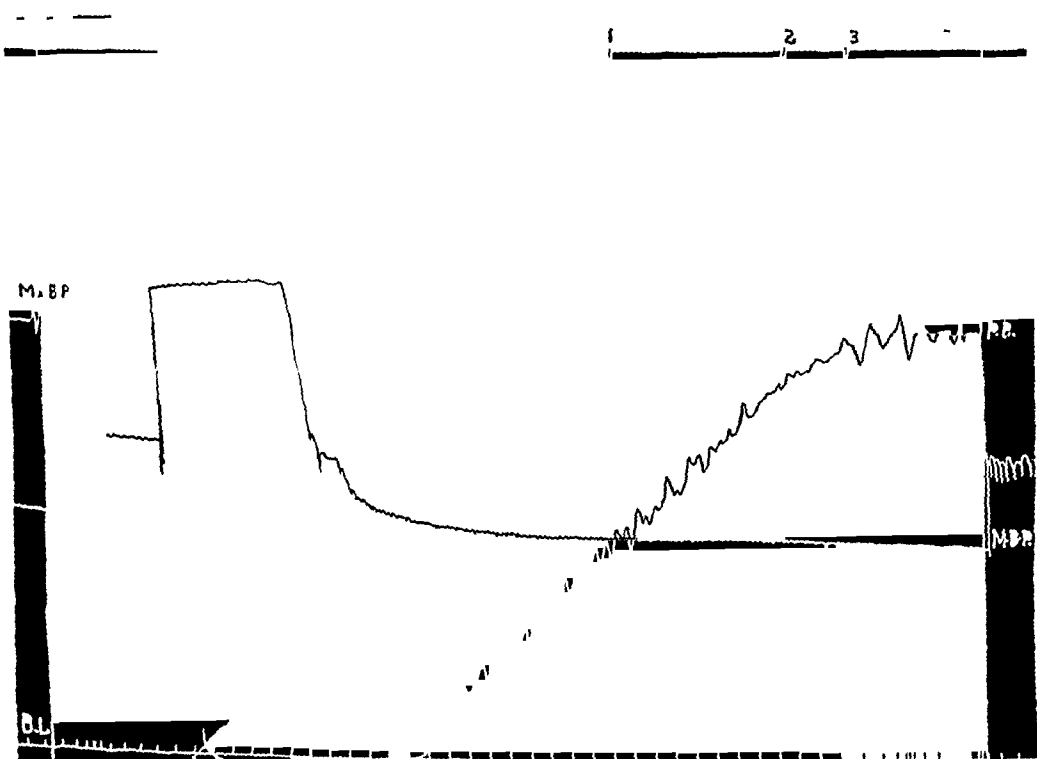


Fig 5—Tracing of auscultatory phenomena See explanation in legend of figure 1

lever of which wrote on a revolving drum. In this pressure system a Dawson maximum and minimum pressure valve was introduced so that the pressure could be held either at systolic or at diastolic pressure. The left femoral artery was exposed freely. Poupart's ligament was cut so as to give as little chance as possible for undue compression. At first the artificial pressure chamber devised by Ettinger<sup>8</sup> was tried, but it failed to work. Two small cups  $\frac{1}{2}$  inch deep were made. From two opposite poles of each cup tubing led off. The rim of each cup on two opposite poles was cut out a trifle. Rubber dam was then tied over each cup rather

loosely and this was connected with a vessel of water which could be raised or lowered and to a mercury manometer which recorded the pressure in mm of Hg. The writing lever was arranged to mark at, or very near the blood-pressure marker. A timer on the base line and a lever attached to a key which when pressed, made a mark on the drum record, completed the apparatus. An assistant held in place the cups one above, one below the artery, another manipulated the drum and the pressure bottle and I listened over the femoral artery, distal to the point of compression using a stethoscope with a small bell. Records were made with descending and ascending pressure.

A typical record was made as follows. The compression chamber was securely held around the femoral artery and the stethoscope placed from

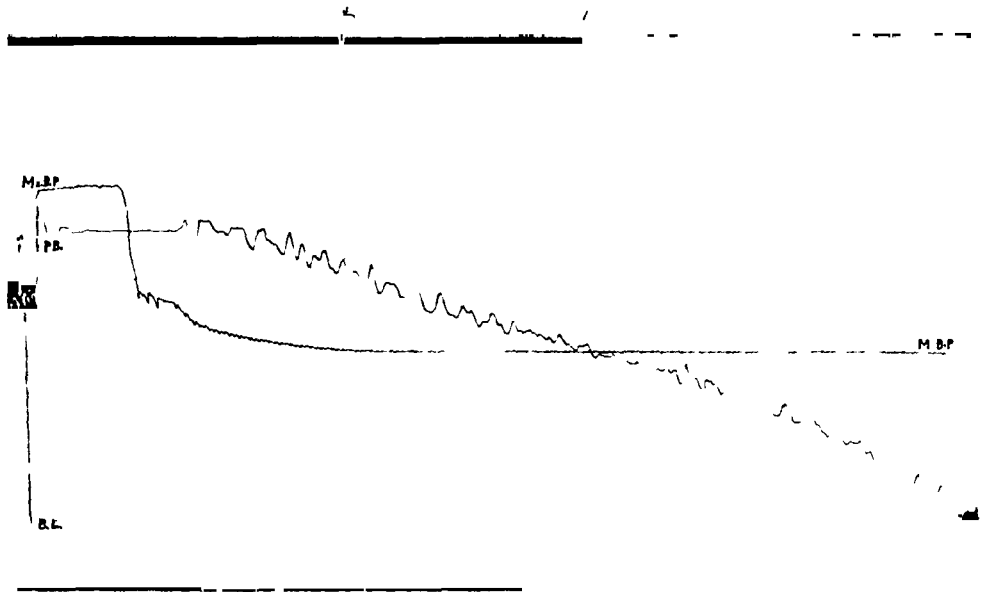


Fig 6—Drawing of auscultatory phenomena. See explanation in legend of Figure 1.

2 to 3 cm below on the skin or muscle directly over the artery. The pressure in the bulb was now raised above systolic pressure, the drum started, the maximum and minimum valve turned to minimum and the bulb gradually lowered. It was impossible to lower this vessel gradually without giving irregular waves on the kymograph. Without being able to see (my back was to the drum) I pressed the marker key (the line at top of all records) when there was change of sound and called the diastolic when I heard the tone change at the time the key was pressed. The object was to find if a certain definite change of tone was coincident with the diastolic pressure. When the line made by the lever of the pressure-bulb connection crossed that of the diastolic pressure it was thought that a

change of tone might occur which could be recognized as corresponding to the diastolic pressure. The study of the records from the three dogs shows that this was possible both with ascending and descending pressure.

The sounds in an artery of a dog as pressure is released and more and more blood flows through the compression site are not like those of man. There are several reasons for this. In the first place, the artery (except in very large dogs) is smaller than the brachial artery of man. It is known that the Korotkoff tones cannot, for example, be heard over the radial artery. The artery must not only be of some size, but it must be so situated that the stethoscope bell can be actually placed over it on the

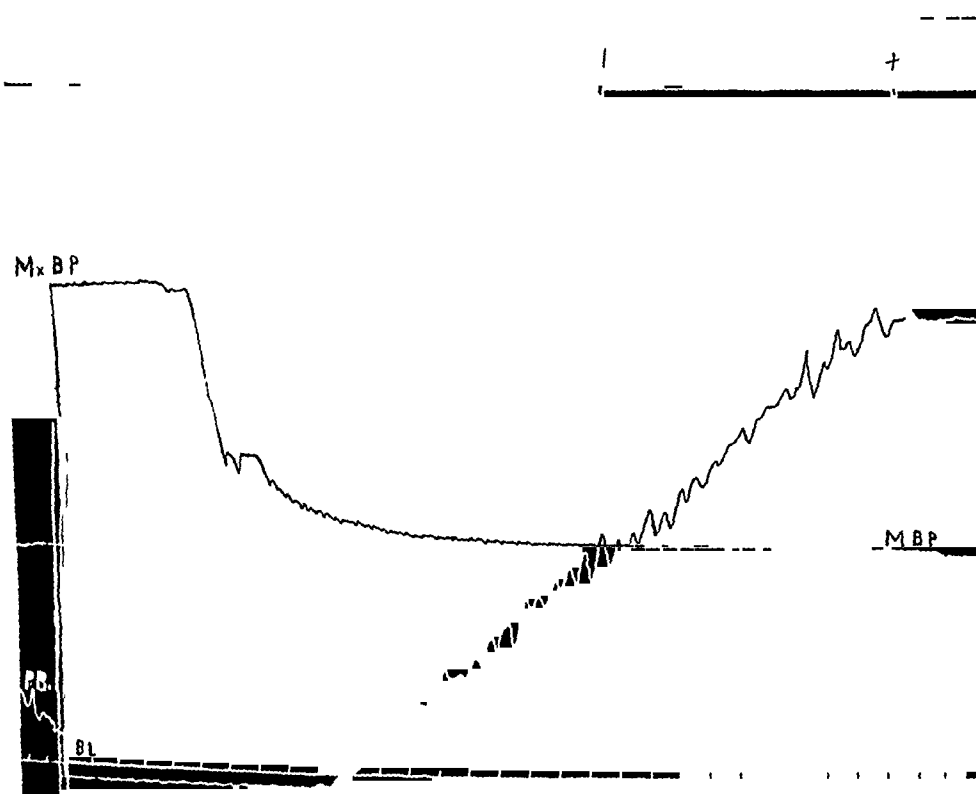


Fig 7—Tracing of auscultatory phenomena. See explanation in legend of figure 1.

skin without compressing the vessel. In the second place, the femoral artery is almost directly in a line with the aorta, and there is only one large branch (the internal iliac) which receives a comparatively small amount of blood. The velocity in the femoral, especially when there is vasodilatation, is almost equal to that in the aorta. The tones depend on velocity of blood flow through the artery for their production (Fischer, Ettinger, etc). Therefore in an anesthetized dog with marked vasodilatation there may be a sound even when no compression is made on the artery comparable to the sound heard in aortic insufficiency in man when the pulse-pressure is practically equal to the systolic pressure. In the

third place, there is a marked vasodilatation in the circulation of an etherized dog, the peripheral resistance becomes less, the systolic pressure is at the same time raised so that at each systole of the heart the blood rushes into a partially collapsed vessel and distends it to its utmost. Erlanger<sup>6</sup> has already shown that such a condition produces a shock and a sound.

Every one of the three dogs showed differences of tone on releasing the compression around the artery. It was necessary to spend some time learning the quality of the tones in order to determine (1) the characters of the tones heard (2) the sequence of the cycle of tones. From twelve to eighteen observations were made on each dog.

Doc 1—May 17, 1912. Fox terrier dog, weight 10 kilos. With pressure rising from 0 (Fig. 1) the first tone heard in this dog's femoral artery was a dull tone which exactly corresponded to diastolic pressure—that is, where the pressure on the artery equaled the minimum pressure in the other femoral artery. This dull tone soon gave place to a sharp clear tone at mark 2. There was then a series of murmurs to be heard ending in a tone at mark 3, somewhat similar to the first tone heard.

It will be noted that practically all tones are present in this particular artery although it was extremely difficult to differentiate them on account of the comparatively faint sounds. Only the lower and upper 1 and 3 were easily made out. On the records the position of 2 was variable. The first dull tone occurred at diastolic pressure in this series; the last dull tone occurred at or near systolic pressure. In the second series from the same animal two figures are shown. It was found difficult always to catch the first sound at systolic pressure by the decrease of pressure corresponding to continuous escapement. Thus in Figure 2 it is seen that the first mark heard is at a point below the maximum pressure, whereas the second mark records the change of tone corresponding to the change in man from the third to the fourth phase, and the third mark is at the disappearance of all sounds. This record shows clearly that the change of tone occurs practically at diastolic pressure and the disappearance of sound is well below the diastolic pressure.

In Figure 3 of this series a slightly different record is seen where the first sound, which was carefully listened for, occurred at maximum pressure and again the change from sharp to dull occurred just at diastolic pressure. The stethoscope was removed before all sound had ceased. There is thus no mark for the disappearance of sound.

This animal was the most satisfactory of the three, as there was the sharpest differentiation of the sounds although the sounds were faint and absolute quiet was necessary in order to hear them and a number of records taken all showed the same correspondence between the change of the sharp tone to the dull tone at diastolic pressure.

Dog 2—May 17, 1912 Bitch, weighing 11 kilos Figure 4 is a typical record among a number taken from this animal The first sound heard is indicated at the mark 1 and corresponds to maximum pressure The second mark was at or near the point of maximum intensity of the clear sound This suddenly became dull at mark 3 which is at diastolic pressure and at mark 4 there was a disappearance of all sound below maximum pressure No records were taken from this dog with ascending pressure

Dog 3—June 5, 1912 Collie weighing 20 kilos This animal did not prove very satisfactory There was an exceedingly high blood-pressure, evidently due to the ether The heart though normal beat powerfully and the pulse pressure was 130 mm Hg, as much as the usual maximum pressure It was impossible to get a disappearance of all sounds However, in the first series (Fig 5), as an example, the first change of tone as the pressure was raised from 0 is seen to be directly at diastolic pressure As it was not possible to raise the pressure bulb up high enough to compress the artery completely, the systolic sound could not be obtained from any of the records

In series two of which Figure 6 is an example, it is seen that the artery was not completely compressed At X was a loud sound probably corresponding to the third in man, before that there was a sound murmur phase At 1 there was a noticeable sudden dulling of the tone which gradually faded off into the tone heard over even the uncompressed artery It is seen that this mark 1 is just at diastolic pressure

It has not been possible to carry further a larger series, nor does it seem of any advantage, since the three animals showed, with minor variations in individual tones the same essential features

#### SUMMARY

There are auscultatory tone phases in the femoral arteries of dogs which correspond in a general way to those in man The systolic pressure is at the point where the first tone is heard as the blood rushes under the site of compression The diastolic pressure is not at the point of disappearance of sound when the pressure is gradually reduced or at a point corresponding to that (as in Dog 3), but occurs when the first dull tone is heard following a loud, sharp tone

It is possible in dogs to measure accurately the diastolic pressure by the auscultatory phenomena, using as the point of diastolic measurement the sudden change of tone from the maximum sound heard to a dull sound It is therefore concluded that the point where diastolic pressure should be read is at the tone change from clear to dull, not at the point where all sound disappears This is, as a rule an appreciable interval below diastolic pressure In man this point where diastolic pressure should be read is just at the point where the third clear tone phase suddenly becomes a dull sound

The author wishes to express his thanks to Prof Easter and to Dr Meek without whose active interest and cooperation the research would have been impossible

Goldsmith Building



# THE PERSISTENCE OF ACTION OF THE DIGITALINS \*

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An attempt has been made in the present research to determine approximately the length of time during which the action of several of the digitalins persists after the introduction of suitable doses directly into the circulation with the hope of throwing some light on their so called cumulative action.

One finds many references in the literature to this so-called cumulative action of the digitalins but there have been few investigations of the phenomena other than clinical.

The term cumulation is used somewhat loosely but it is generally understood to mean the action which is manifested rather suddenly after the continued use of doses which singly do not cause perceptible effects.

Van der Heide<sup>1</sup> states that Megevaud was the first to study this subject by means of animal experimentation in 1879 but the research was incomplete, so far as cumulation was concerned since that investigator was interested mainly in the histologic changes induced in certain organs during chronic digitalis poisoning.

Schmiedeberg<sup>2</sup> states that the three digitalis principles digitalin, digitalin and digitoxin are absorbed with relative difficulty and slowly excreted, and on these factors the so-called cumulative action of digitalis is dependent in part in part on a storage of the active substance in the organism when digitalis is used for prolonged periods during renal disturbance.

These deductions of Schmiedeberg's appear to be based on theoretical considerations, at least I am not aware of any experiments on which they are based directly, and certain of the digitalins appear to be excreted through the gastro-intestinal tract to a greater extent than through the kidneys.

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Read in the Section on Pharmacology and Therapeutics of the American Medical Association at the Sixty Third Annual Session held at Atlantic City, June 1912.

From the Laboratory of Pharmacology, Cornell University Medical College, New York.

The expenses of this investigation were borne in part by the Therapeutic Research Fund of the American Medical Association.

1 Van der Heide Arch f exper Path u Pharm, 1885 vii 127

2 Schmiedeberg Arch f exper Path u Pharm, 1883 vii 185

3 Hatcher Am Jour Physiol, 1909, xiii, 303

Van der Heide<sup>1</sup> investigated the cumulative action of helleborein after injecting it subcutaneously into rabbits, and that of digitalin and helleborein administered to dogs by the mouth and rectum, and subcutaneously

Owing to his employment of these several modes of administration, and of varying amounts of the drugs at irregular intervals, and even of both drugs in the same experiment, in some instances, it is difficult to form a correct opinion of the value of the conclusions at which van der Heide arrived. His results are complicated still further by the fact that he used an impure digitalin, which consisted of digitalein mainly, and this was dissolved in a 3 per cent infusion of digitalis for subcutaneous injection, hence his results are due to the use of digitalis rather than to true digitalin, in those experiments where helleborein was not employed.

Van der Heide calls attention to the fact that the word cumulation indicates that the phenomena were attributed to a storage of the active principles in the organism, but he remarks that the earlier writers had no very clear conception of the method by which storage took place, and I might add that the same degree of uncertainty still exists.

He concluded that the dog and rabbit showed cumulative symptoms so far as the cardiac effects were concerned, and habituation on the part of the nervous system.

The next important pharmacological investigation of this cumulative action of the digitalins was made by Fraenkel,<sup>4</sup> who administered several of the digitalins to cats by subcutaneous injection and attempted to observe the cumulation by means of the slowing of the pulse-rate, by the onset of gastro-intestinal symptoms, and by the death of the animal, following the repeated injection of doses which were individually too small to produce these effects.

Fraenkel's conclusions have been quoted very frequently, but I believe that he made important errors, and, since certain of his statements are irreconcilable with mine, it will be necessary to discuss some of his experiments later in connection with my own.

Cloetta<sup>5</sup> tried to estimate the storage of one of the digitalins in the hearts of frogs and rats which had been poisoned with large amounts of the drug, but he was unable to detect even traces of the poison in that organ.

Schlomonsun<sup>6</sup> found that a group of substances (alcoholic phosphatide) could be isolated from the hearts taken from the human cadaver and from the dog, and that these substances appeared to possess an especial capacity for combining with the digitalins chemically, while the

<sup>4</sup> Fraenkel *Arch f exper Path u Pharm*, 1903, li, 84

<sup>5</sup> Cloetta and Fischer *Arch f exper Path u Pharm*, 1906, liv, 294

<sup>6</sup> Schlomonsun *Arch f exper Path u Pharm*, 1910, lxi, 294

corresponding fractions obtained from the livers and skeletal muscles had no such affinity

This observation of Schliomensun's would seem to indicate the possibility of storage of the digitalins in the heart

Straub<sup>7</sup> concluded that no storage of ouabain occurred in the tissues of the heart, as a result of his perfusion experiments, in which he found that the poison could be washed from the heart before it stopped beating by merely substituting fresh Ringer's solution for the poisoned perfusion fluid

Lhoták von Lhota<sup>8</sup> studied chronic digitalis poisoning induced in rabbits by oral and subcutaneous administration, and concluded that rabbits showed cumulative effects up to the tenth day of the poisoning, and tolerance thereafter

The use of the rabbit for this type of experiment, and the employment of the digitalins by oral and subcutaneous administration for these investigations will be discussed in connection with my own results with such experiments

#### CAUSES OF ACCUMULATION, SO-CALLED

Absorption and excretion play an important rôle in the so-called cumulative actions of the digitalins, but it is an extraordinary fact that we know almost nothing about either of these processes, except that the rate of absorption of these bodies from the alimentary tract is variable

One finds extremely loose statements in the literature concerning the length of time during which the digitalins remain in the blood-stream after their introduction into the circulation, but so far as I have been able to learn these statements are not supported by experimental evidence, and the crude attempts made by van der Heide to detect the digitalins in the organs and the circulating blood are hardly worthy of mention, but the matter assumes much importance in view of the statement made by Straub,<sup>7</sup> that the standstill of the perfused frog's ventricle depends on the concentration of the poison in the perfusing fluid and not on the total amount which passes through the heart, and that during perfusion no storage (in the common acceptation of the word) takes place in the tissues of the frog's heart

It may be stated here that experiments still in progress in our laboratory show that practically all of a fatal dose of ouabain leaves the blood-stream within about three minutes after its injection into the veins of a cat and we have also found that the cat's heart is poisoned promptly when ouabain is injected in extremely dilute solutions (1-250,000) at such a rate that its dilution in the blood-stream must be less than one in five hundred millions if it leaves the circulation as rapidly under these

7 Straub *Biochem Ztschr*, 1911, xxx 392

8 von Lhota, L *Arch int de pharm et de therap*, 1910, xv, 451

conditions as it does when it is injected more rapidly, and if such is the case there can be little doubt that the action of ouabain on the intact mammalian heart depends on the total amount which passes through the heart, and not on the concentration in which it exists in the blood, for the concentration just mentioned is vastly less than that which Straub found necessary to bring the perfused frog's heart to a standstill

The slowing of the pulse-rate and the cardiac irregularity, which may be induced in many animals by the continued use of suitable doses of the digitalins have been utilized by several observers for the study of the onset and duration of the digitalis action, but it is true, nevertheless, that the effects of digitalis on the heart-rate in the cat are quite variable and many of my myographic tracings, taken at various intervals of time following the intravenous administration of large doses of the digitalins, give no visible evidence of their action on the heart, and in many cases these tracings are in no way different from those taken from normal animals, but it is impossible to suppose that the digitalins so administered have produced no *action* whatever, though the *effects* of such action are not perceptible in the tracings

Even in those animals in which digitalis causes slowing of the pulse rate, that effect is induced only after the administration of fairly large doses. If, for the sake of illustration, we accept 25 per cent of the fatal dose as the minimum amount which will be required in a given case to slow the heart-rate appreciably, it follows that this effect will persist only until elimination has reduced the amount in operation to a point where it becomes ineffective, at which time even a small dose will suffice to raise the amount in operation to the effective point and slowing will be induced again, for the smallest dose which produces measurable symptoms must consist of fractions which singly are insufficient to produce measurable effects

This latent digitalis action often escapes attention in man and it may then become the basis for the so-called cumulative action, because of the small additional amount of the drug which then suffices to raise the action to the level where toxic symptoms are manifested

This is understood readily when one remembers that the full therapeutic effect of digitalis is separated from the toxic action only by an imaginary line

Briefly, then, one may investigate the so-called cumulative action of the digitalins by studying their absorption and excretion, by determining the length of time during which these principles remain in the blood-stream after they have entered the circulation, he may study the question of their storage in the tissues, particularly in the heart and nervous system. He may attempt to determine the duration of action by observing the objective symptoms, such as the slowing of the pulse-rate and the

cardiac irregularity, which they induce, as Fraenkel did, or, he may estimate directly the degree to which the previously administered drug is still effective, and the length of time during which the action persists.

As a matter of fact, while casting about for the best means of investigating the subject I have experimented along nearly all the lines just mentioned, but the methods which I have employed are quite different from those used previously, and the results of these investigations will be published in a series of papers.

In the research with which this paper deals I have attempted to estimate the latent action of the digitalins as well as that which induces symptoms which are readily observed, in other words I have tried to determine the length of time during which the action of a single large dose, or repeated doses of these bodies persists, and the relative intensity of the persisting action after a given interval of time.

#### TECHNIC

The following method was used in estimating the persistence of action of the digitalins in the cat and dog in the larger number of experiments which I have to report.

The fatal dose of the digitalis body for a given species was determined in a series of experiments in which the drug was injected slowly and continuously from a buret into the veins of the animals until death resulted after the typical symptoms of digitalis poisoning.

Having thus determined the fatal dose of a digitalin, a toxic, but not fatal, dose of the drug in measured amount was injected from a hypodermic syringe into the veins of a normal animal, which was then kept under observation for the required period of time, varying from one to thirty days. The animal was then placed on the operating board and the amount of the drug which was then required to cause death was determined in the way just described for a normal animal.

The difference between the fatal dose for the test animal which had previously received the initial dose and that required by a normal animal of the same weight must be due to the persisting action of the initial dose.

The following, taken from the protocol of an experiment, will serve to illustrate this method of estimating the persistence of action of digitalis.

May 16, 1912 Cat, female, weight 2.55 kg, 11 31 a m, heart-rate 248 per minute, 11 31½, heart-rate 207 per minute, 2 45 p m, heart-rate 210, cat much excited, 2 55, injected 80 mg digitalis per kg by vein, 4 05, emesis.

May 17 10 32 a m, animal depressed, heart-rate 258 252

May 18 10 05 a m, appears nearly normal, heart rate 210

May 20 1 25 p m, appears quite normal, heart-rate 256

May 24 10 00 a m, anesthetized, digitalis injected slowly by vein, 10 48, toxic symptoms, injection stopped, 10 52, animal died, 62 mg digitalis per kg of body weight had been injected.

A normal cat requires a dose of 100 mg of digitalis per kg of body-weight to cause death, but the test animal in the experiment just cited required only 62 mg per kg — a difference of 38 mg per kg — which represents the persistence of action of the initial dose after an interval of eight days.

I have used ouabain (the so-called crystalline strophanthin of Thoms) for estimating this latent action of the digitalis principles in nearly all of the experiments recorded in Tables 1 to 5, inclusive, and Table 7 and 10, because of the greater accuracy which is permitted by its use. When ouabain was not used the fact is so stated in the footnotes accompanying the tables.

The use of ouabain in this way is based on the results obtained by Hatcher and Brody,<sup>9</sup> who found that ouabain and the various digitalins were capable of replacing each other in the estimation of the fatal dose, for example, if 50 per cent of the fatal dose of digitoxin and 50 per cent of the fatal dose of ouabain were injected into the veins of a cat the effect was the same as that which followed the injection of a fatal dose of either ouabain or digitoxin alone, except for the fact that when ouabain was used with digitoxin in this way death resulted more promptly than when digitoxin was used alone, because of the comparative slowness with which just fatal doses of digitoxin act, whereas ouabain acts promptly when just fatal doses are administered, and, curiously, the combination of fractional doses of digitalis or digitoxin with ouabain also acts promptly.

This permits of greater accuracy in the estimation of the fatal dose of digitalis or digitoxin than would be possible were either of those bodies used alone in the manner previously described.

The employment of ouabain also permits of a more accurate determination of the latent action of digitoxin, digitalis and other digitalins, than would be possible by means of those digitalins themselves for the final test, and furthermore, the insolubility of certain of these principles, such as digitoxin and digitalin, interferes with their slow and continuous intravenous administration.

The following protocol (in brief) of an experiment illustrates this method of estimating the latent action of a digitalin.

April 16, 1912 Cat, gray striped, female, weight 2.2 kg 3 35 p m, 0.4 mg digitoxin per kg in 3.2 cc 6 per cent alcohol, by vein, 4 15, emesis, 4 25, convulsion 4 50, symptoms suggest that dose is fatal.

April 17 3 15 p m, attempts to vomit, death seems imminent.

April 20 9 30 a m, weight 1.9 kg, heart is very rapid, 11 22 ouabain in 1 100 000 solution, by vein, 11 49, death after 0.026 mg ouabain per kg, or 26 per cent of the average fatal dose.

Since the animal received 26 per cent of the average fatal dose of ouabain four days after the initial dose of digitoxin, it follows that 74 per cent of the fatal dose was attributable to the persistence of action of the digitoxin.

When the interval between the first dose and the final test is only a few hours or a day the sum of the amounts injected is almost the same.

<sup>9</sup> Hatcher and Brody, *Am Jour Pharm* 1910, LXVIII 360.

as that which would be required at a single injection to cause death because the effects of a fairly large dose of digitalis or digitoxin persist almost unchanged for a day

When the interval following the administration of a given initial dose is as much as a week the amount required to cause death at the time of the final test is somewhat variable because elimination takes place at very different rates in different animals, but even as late as a month after the intravenous injection of a nearly fatal dose of digitalis the test animal may require less than a normal animal would to cause death showing that the action of digitalis sometimes persists even after such a long interval during which there has been no drug administered

#### NATURE OF PERSISTING ACTION

It will suggest itself at once that this difference between the amount required to kill the normal, and that required to kill the test animal after such a long interval of time is to be attributed to inquiry which the heart has sustained from the initial action of the digitalis rather than to any digitalis still operating on the heart

Against such an argument is the fact that the cat's heart may be poisoned to an equal degree with ouabain and after an interval of twenty-four to forty-eight hours following a nearly fatal dose the animal behaves like a nearly normal one, requiring almost as large a dose to cause death as a normal animal of the same weight would require

The rabbit may be given a very nearly fatal dose of digitalis or digitoxin (the action of which is extremely persistent in the cat) but after two or three hours, the heart has so far recovered its normal condition that it will require a full fatal dose to cause death

One might suppose this rapid elimination of digitoxin and digitalis by the rabbit to be due to habituation but it follows the first dose

It is difficult to account for the great differences in the persistence of action of the several digitalins in the same animal, or in that of the same digitalin in different animals, except on the hypothesis that the digitalins are eliminated at very different rates

I have determined the fatal dose and the persistence of action of a number of the digitalins for the cat in the manner described, and have attempted to carry out similar experiments on other animals, including the dog, rabbit and guinea-pig, with some of the more important members of the digitalis group, but this was not feasible and a different procedure had to be adopted with the rabbit, while the attempt to use the guinea-pig for the experiments was abandoned

The white rat shows nervous symptoms following the injection of large doses of digitoxin, and these symptoms appear to overshadow the cardiac action. The phenomena have not been investigated by us, but it was observed that slight stimuli, such as are induced by a sudden noise, or touching the cage, were followed by violent strychnin-like reflexes, and clonic convulsions which gradually subsided. Later the convulsions were absent, but a slight stimulus gave rise to violent trembling. These symptoms are present in a mild degree in the rabbit after large doses of digitoxin.

The action of digitoxin is more persistent than that of other principles of this group, and since its action persists for only a few days in the dog it seemed to be hardly worth while to test the more rapidly eliminated digitalins on that animal.

I believe that the cat behaves more like man toward the digitalins than does any other animal which is available for these experiments, hence the cat has been used in much the larger number of my experiments.

The results obtained in these experiments on cats and dogs are given in Tables 1 to 7, the experiments on rabbits will be considered later.

In these tables the initial dose, the dose required to cause the death of the animal after the interval of time following the initial dose, and the persistence of action are all expressed in percentages of the average fatal dose for the normal animal.

As previously stated, the figure which expresses the persistence of action is gotten by subtracting the figure representing the dose required after the interval following the initial dose, from 100 per cent. Thus the first animal of the first series of Table 1 required 83 per cent of the average fatal dose for a normal animal to cause death after an interval of one day after the initial dose, hence the persistence of action in that case was equal to 17 per cent of the average fatal dose for a normal animal of that size.

The arrangement used in the tables is intended to facilitate the study of the results obtained, for it would be necessary for the reader to consider such doses as 0.1 mg, 575 mg and 70 mg, if actual doses were given expressed in mg per kg of weight.

The fatal intravenous dose of each of the digitalins used for each of the species of animals employed in this research may be found in Table 11. These doses are expressed in mg of the drugs per kg of body weight of the animal, and from these doses may be calculated the dose used in any experiment should anyone care to do so.

Onabain was used in freshly prepared solution in the final test of the persistence of action as previously stated, in most of the experiments and where it was not used the fact is stated in a footnote.



TABLE 1—PERSISTENCE OF DIGITALIS ACTION IN CATS

Experiment	Initial Dose Per Cent of Fatal	Dose Required After Interval	Persistence of Action Per Cent of Fatal	Interval in Days
SERIES 1				
1-B	50	83	17	1
2-B	50	56	44	2
3-B	50	50	50	3
4-B	50	54	46	4
5-B	50	110	—10	7
6-B	50	75	25	7
7-B	16.5×2	81	19	4
8-B	16.5×2	77	23	9
9-B	16.5×2	79	21	21
10-B	40	92	8	29
SERIES 2				
39	96	115	—15	28
40	108	74	26	29
43	100	32	68	11
44	100	42	58	11
49	100	52	48	10
50	100	77	23	9
SERIES 3				
4	45	62	38	33
5	45	45	55	34
6	40	117	—17	33
7	10	76	24	33
15	45	64*	36	9
16	45	76*	24	9
35	60	122	—22	14
36	84	73	27	12
37	60	84	16	28
38	60	88	12	28
SERIES 4				
1-S	75	51	49	30
2-S	75	77	23	30
3-S	75	81	19	21
4-S	75	68	32	21
5-S	75	67	33	10
6-S	75	91	9	5
7-S	75	67	33	5
8-S	75	38	62	5

\*Digitalis used for final test

## DISCUSSION OF TABLE I

The scheme of tabulation used here was not intended at the time the experiments were made, hence the numbers assigned to the experiments are not in sequence. Some of the animals died during the interval following the initial dose, as in series 2, in which six of the twelve died. The initial dose in these twelve experiments was intended to be as nearly fatal as possible without actually killing the animals.

The animals used in experiments 7-B to 9-B received two initial doses, each being 16.5 per cent of the fatal, on two successive days, and in those experiments the intervals are reckoned from the dates of the first doses.

Some animals required more than 100 per cent of the average fatal dose after the specified interval of time, such animals being tolerant, while in some other cases the amount required to cause death is quite as far below the amount which we would expect as those just cited are above it. Such individual differences are always seen in biological testings, but Experiments 4 and 5 of the third series require individual consideration. In both of these cases the animals were either very susceptible, or there was some error in technique.

Aside from the examples just mentioned there are great irregularities to be observed in the doses required to cause death after the intervals of time following the initial doses, and this is to be expected in view of the fact that there are two interacting causes of these irregularities.

Since these figures will receive the closest scrutiny and possibly the severest criticism, it will be worth while to discuss them here briefly.

In Experiment 1-S of the fourth series the animal required only 51 per cent of the average fatal dose after an interval of thirty days following an initial dose reckoned at 75 per cent of the fatal, and in 6-S of the same series 91 per cent of the average fatal dose was required to cause death after an interval of only five days following an initial dose of the same amount as that received by the animal previously mentioned.

Such discrepancies appear at first glance to render the results almost useless, but a simple calculation will suffice to show that a comparatively slight difference in susceptibility on the part of one animal, and of tolerance on the part of the other, will explain even these great variations from the average.

If we suppose that the first of these two animals was susceptible to such a degree that it would require 20 per cent less than the average fatal dose to cause death (and it could not have been much more susceptible, because it survived 75 per cent of the average fatal), we shall have the following equation for this experiment:

Fatal dose, 80 mg per kg    initial dose (75—80=) 94 per cent of the fatal,  
dose required after interval (51—80=) 64 per cent of fatal, leaving persistence  
of action equal to 36 per cent of fatal.

This would not be far from what we might expect in case the elimination was slower than normal in this animal. In the same way we may explain the unusually slight degree of persistence of action in the case of the other animal. If we suppose that this animal was tolerant to such a degree that it would require 20 per cent more than the average fatal dose to cause death we would then have the following equation:

Fatal dose, 120 mg per kg of body weight, initial dose  $(75 - 120 =) 62.5$  per cent of fatal, dose required after interval  $(91 - 120 =) 76$  per cent of fatal, leaving persistence of action equal to 24 per cent of fatal

This would be far nearer the amount which we should expect than that shown in the table

It was found after completion of the experiments that intervals of three weeks and more were too long except when they followed the very largest initial doses, because they prolong the average of the duration of action unduly when they follow doses smaller than those which the animal just survives

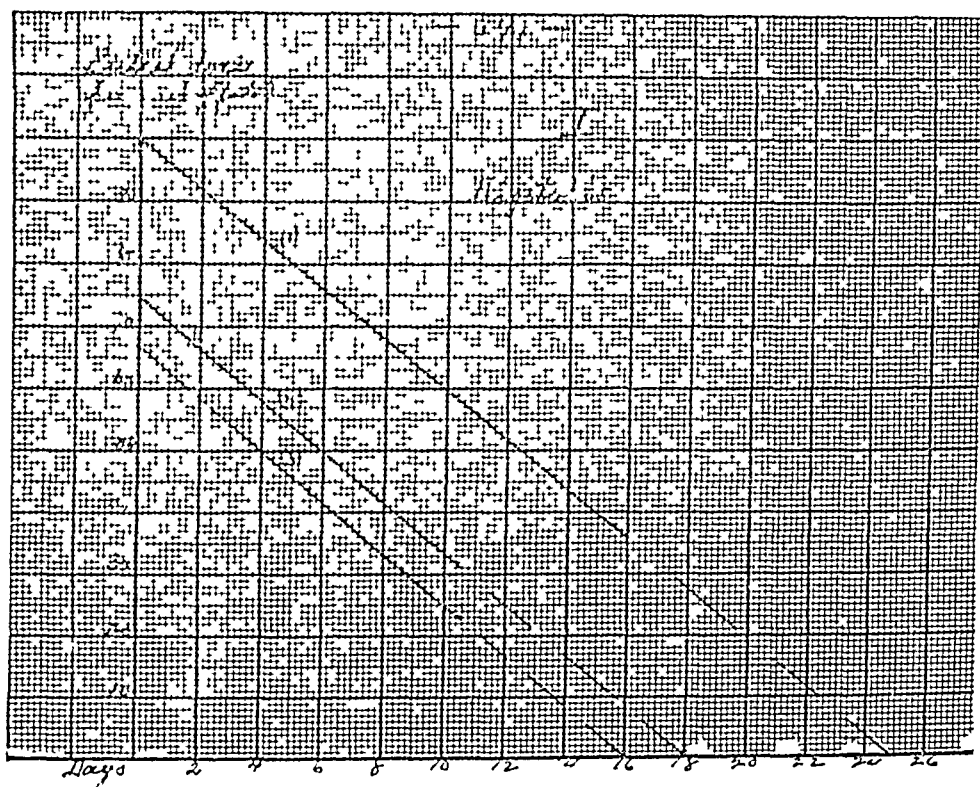


Diagram 1—Showing persistence of action of digitalis. Upper line based on experiments in Series 2 of Table 1, middle line based on six experiments in Series 4, Table 1, lower line based on all experiments in Series 2, and all others in Table 1, except those in which interval is four weeks or more

Reference to the several tables will show that the cat, dog and rabbit, manifest the persistence of action of digitoxin in the order of their susceptibility, as illustrated in Diagram 6, and I have gained the impression that individuals of the same species exhibit a similar relationship between these factors, the more tolerant individuals seeming to show less persistence of action after similar intervals than the more susceptible after doses which are relatively equal so far as one can judge by objective symptoms (See discussion of Table 6)

The averages of the results of the experiments given in several of the tables are shown diagrammatically. In these diagrams the unbroken lines indicate the decline of the action between the initial doses and the time of the final tests, and they are then continued as broken lines. While it is very probable that the elimination should be represented more accurately by curves, I have no data for the construction of such curves.

Eight of the ten experiments in the first series of Table 1 give the following averages. The initial dose was 45 per cent of the fatal, the interval was about four days, and the persistence of action was equal to about 27 per cent of the fatal. The entire series gives an interval of nine days, with persistence of action equal to 25 per cent of the fatal, indicating a persistence of action far beyond that which we should expect with such doses.

TABLE 2—PERSISTENCE OF DIGITOXIN ACTION IN CATS

Experi- ment	Initial Dose Per Cent of Fatal*	Dose Required After Interval	Persistence of Action Per Cent of Fatal	Interval in Days
SERIES 1				
2	50	45	55	5
3	50	48	52	5
4	50	71	29	10
5	50	75	25	10
20	66	33	67	6
21	50	76	24	15
22	50	90	10	14
23	33	88	12	14
24	33	78	22	14
25	33	70	30	14
SERIES 2				
1-D	60	66	34	1
2 D	100	37	63	2
3 D	60	71	29	8
4 D	60	40	60	7
5 D	80	26	74	4

\*The fatal dose of the specimen of digitoxin used in the first series was 0.3 mg per kg of body weight, that of the specimen used in the second series was 0.5 mg per kg.

The initial dose in the second series of experiments is reckoned at 100 per cent of the average fatal, but, as previously stated, six of the twelve animals intended for this series died, and those which survived were slightly tolerant, hence the persistence shown is less than we should expect with such doses. After deducting the 15 per cent excess of the usual fatal dose, taken by animal No. 1, we have an average of 36 per cent of the fatal dose persisting after an average interval of sixteen days. (Lane 1 of Diagram 1.)

There are only four experiments in the third series which should be included in the results because the intervals in the others were too long. For the same reason only six of the experiments in the fourth series should be included in the calculations. These six give an average persistence of action equal to 31 per cent of the fatal dose after an average interval of eleven days (Line 2, Diagram 1.)

Taking all of the experiments in Series 2, and all of the remaining in the table in which the interval is less than four weeks, we have a total of twenty-five experiments with an average persistence of action equal to 23 per cent of the fatal with an interval of eleven days following an average initial dose equal to 67 per cent of the fatal, (line 3, Diagram 1.) The nearly parallel lines of this diagram afford strong evidence that the results are approximately correct.

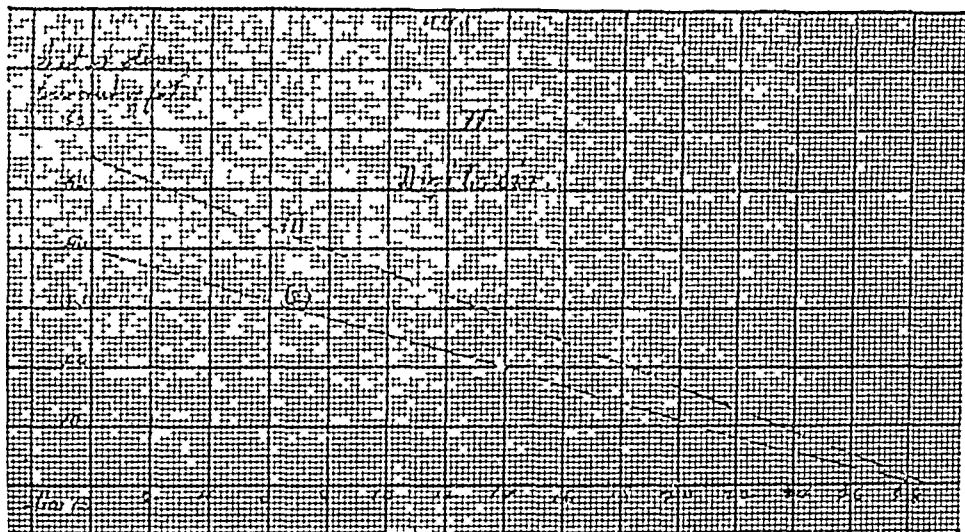


Diagram 2—Showing persistence of action of digitoxin. Upper line based on all the experiments in Table 2, lower line based on five experiments with nearly equal dosage and intervals before the final test.

It is not necessary to call attention to every experiment in which the results are not in strict agreement with the general average but it will be seen at once that four of the animals—2, 3, 20 and 25 of the first series in Table 2—were distinctly susceptible, since they required less in the initial and final doses combined than the average fatal dose. These four experiments prolong the average persistence of the series unduly, but, on the other hand, the first and second animals in Series 2, were just as certainly tolerant, hence the average persistence of this series would be shorter than it should be, and it is believed that the line (1) in Diagram 2 representing the entire number of experiments, sixteen, is very nearly a correct representation of the persistence of action of digitoxin in the cat.

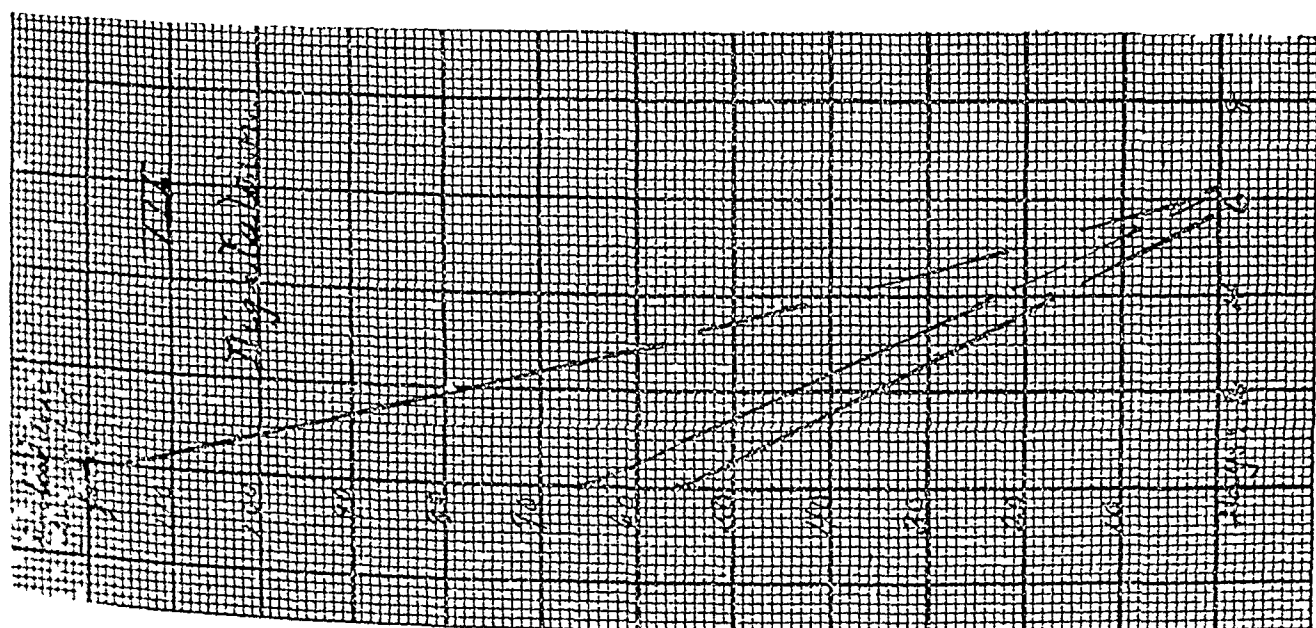


Diagram 3—Showing the persistence of action of digitalin. Upper line based on all experiments in Table 3, middle line based on experiments in Series 2 of Table 3, lower line based on four experiments with nearly equal doses and a uniform interval of time before final test

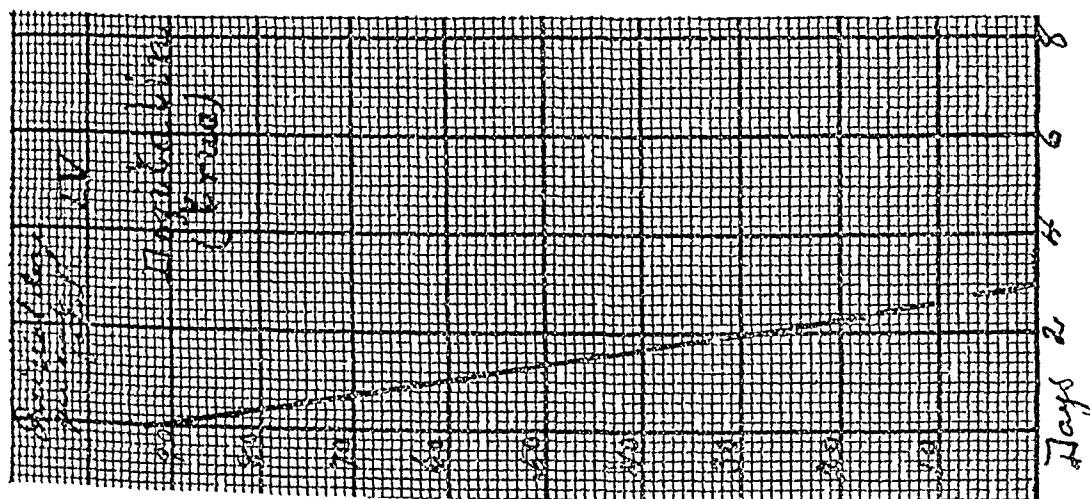


Diagram 4—Showing persistence of action of true digitalin, based on all experiments in Table 4

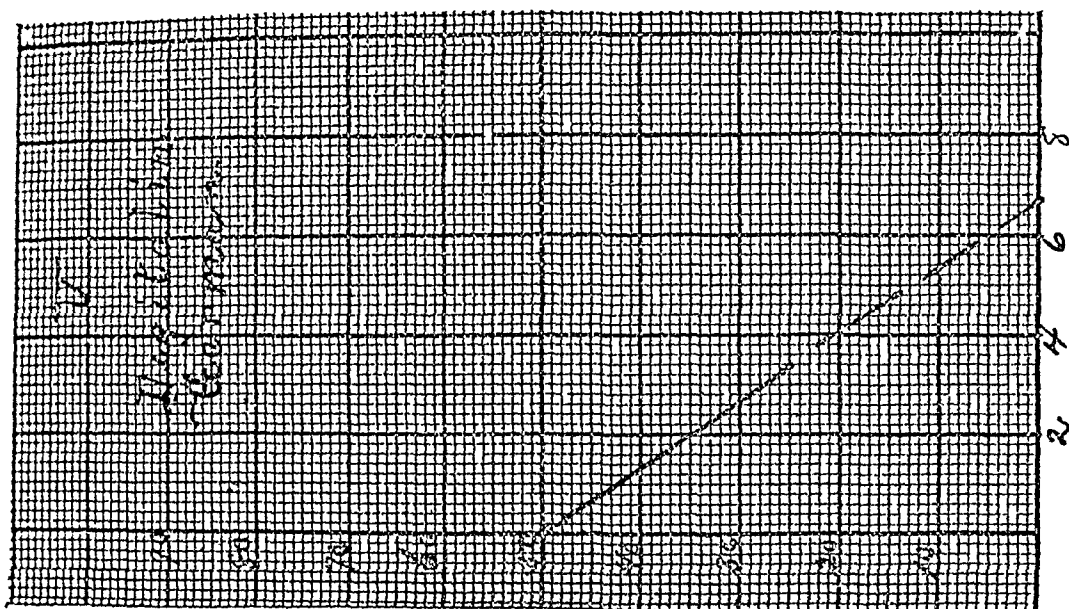


Diagram 5—Showing persistence of action of German digitalin, based on six experiments with uniform dosage (See Table 6)

Line 2 in the diagram, representing the five animals with nearly uniform initial dosage and practically uniform intervals of fourteen days (one fifteen days), is nearly parallel with line 1. None of the fifteen animals failed to show the persistence of action.

TABLE 3—PERSISTENCE OF DIGITALIN ACTION IN CATS

Experiment	Initial Dose Per Cent of Fatal	Dose Required After Interval	Persistence of Action Per Cent of Fatal	Interval in Days
SERIES 1				
26	60	102	— 2	1
27	30	76	24	1
28	50	84	16	1
29	45	96	4	2
30	45	90	10	4
31	60	71	29	1
32	60	83	17	4
32a	60	67	33	2
32b	60	86	14	2
32c	60	86	14	4
32d	60	69	31	4
32e	60	110	—10	14
32f	60	86	14	14
SERIES 2				
32g	45×3*	37	63	3
32h	45×3*	29	71	3
32i	45×3*	56	44	3

\*Three initial doses of 45 per cent of the fatal were given on three successive days in these three experiments, the final test being made on the fourth day.

TABLE 4—PERSISTENCE OF ACTION OF DIGITALIN (TRUE) IN CATS

Experiment	Initial Dose Per Cent of Fatal	Dose Required After Interval	Persistence of Action Per Cent of Fatal	Interval in Days
17	50×2	55	45	2
18	50×2	131	—31	2
20	66	88	12	2
21	66	82	18	2
22	50×2+33	65	35	3
23	33×3	74	26	3

The persistence of digitalin action is shown to be brief in the experiments tabulated here, hence those experiments in which the interval was fourteen days should not be included in the calculation, it will be observed, however, that the sum of the combined doses required by these two animals divided by two gives 98 per cent of the average fatal, as we should expect after the action of the initial dose had ceased.

Diagram 3 shows a close parallelism between the three lines, (1) based on the averages of all of the experiments in both series, (2) that based on the three experiments in the second series, and (3) that based on the four experiments in which nearly equal doses were given, and a uniform period of four days was allowed to elapse before the final tests were made

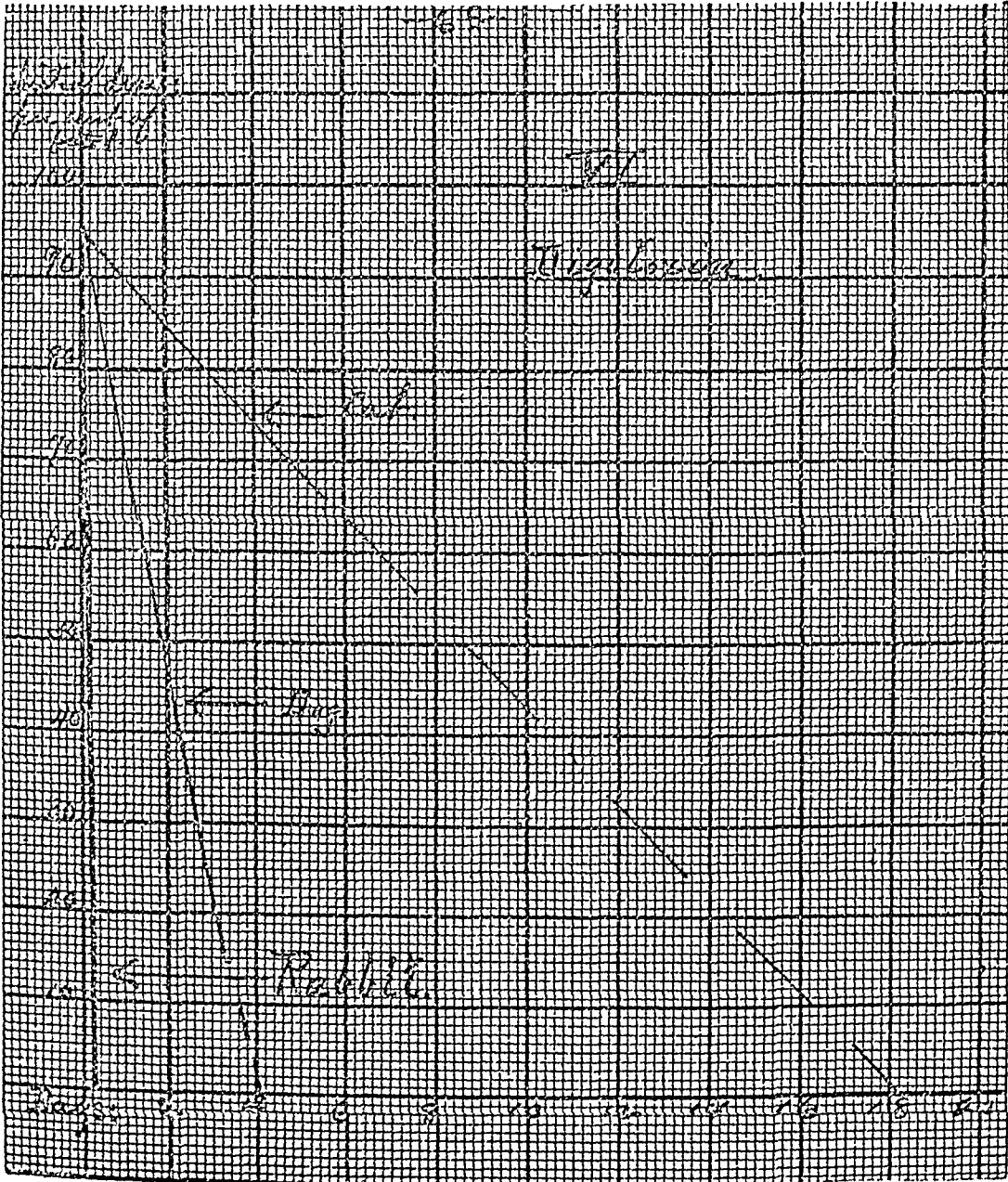


Diagram 6—Showing persistence of action of digitoxin, on the cat (upper line), dog (middle line), and rabbit (nearly perpendicular line)

The diagrams representing the results obtained with German digitalin true digitalin and digitalein are placed together for convenience of comparison



Two initial doses of 50 per cent of the fatal were given on successive days in Experiments 17 and 18, and three initial doses were given on successive days in Experiments 22 and 23, and in all four experiments the final test was made on the day following the last initial dose

In Experiments 20 and 21 a single initial dose was given and the final test was made after an interval of two days

The averages of the six experiments in Table 4 are as follows

Initial dose 94 per cent of the fatal, dose required after an average interval of two and one third days, equal to 82 per cent of fatal, leaving a persistence of action equal to 18 per cent of the average fatal

The averages are represented in Diagram 4

TABLE 5—PERSISTENCE OF ACTION CRYSTALLINE OUABAIN AND STROPHANTHUS IN CAT

Experiment	Initial Dose Per Cent of Fatal	Dose Required After Interval	Persistence of Action Per Cent of Fatal	Interval in Days
CRYSTALLINE OUABAIN				
1	75	85	15	1
2	75	59	41	1
3	75	93	7	1
4	75	54	46	1
5	80	90	10	1
STROPHANTHUS				
1	70	69	31	1
2	55	42	58	1
3	60	56	44	1
4	60	83	17	1
5	75	92	8	1
6	75	107	— 7	1
7	75	80	20	1
8	75	70	30	1

Fraenkel<sup>4</sup> found that digitalin possessed very little of the so-called cumulative action, and this agrees very well with my own results, which are shown in a striking way in the diagram

Ouabain, strophanthin (which is methyl-ouabain) and strophanthus are generally supposed to exhibit the cumulative action to a slight degree only, or not at all

All but one of the animals in the thirteen experiments recorded in Table 5 show some persistence of action after an interval of one day. One of the animals (No 2 of the second series) was evidently unusually susceptible, and one (No 6 of this series) is just as obviously tolerant, but the averages afforded by the experiments show that these drugs belong in the class with true digitalin, so far as the persistence of action is concerned

TABLE 6—PERSISTENCE OF ACTION OF VARIOUS DIGITALINS IN CATS

Experiment	Initial of Fatal Per Cent Dose	Dose Interval After Required	Persistence of Fatal Per Cent of Action	Interval in Days
CONVALLARIA				
40	60	99	1	3
41	75	72	28	1
42	75	92	8	1
43	70	57	43	1
44	75	94	6	1
APOCYNUM				
14	75	94	6	1
15	75	60	40	1
16	75	95	6	4
17	50	86	14	1
18	40	98	2	1
19	50×2	75	25	3
GERMAN DIGITAIN				
16	50	37	63	3
17	50	100	0	3
18	50	47	53	1
19	50	86	14	2
20	50	114	—14	3
22	50	66	34	9
SQUILL				
13	70	80	20	1
14	50×3	54	46	3
15	50×3	30	70	3
16	50×3	42	58	3
17	80	57	43	2
18	80	71	29	2
BLACK HELLEBORE				
11	50	94	6	1
12	50×2'			
13	50×3			
14	50×3	29	71	3
15	80	47	53	2
16	80	51	49	2
17	80	46	54	2
HELLEBOREIN				
7	50	65	35	1
8	50×3*			
9	50×3'			
10	80	36	64	2

\*Fatal

Experiment	Initial of Fatal Per Cent Dose	Dose Interval After Required	Persistence of Fatal Per Cent of Action	Interval in Days
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## OUABAIN

8	44	64	36	1
9	70	68	32	2
10	70	74	26	2
11	45+50	73	27	2
12	45+50+50	39	61	3
13	80	89	11	2
14	80	73	27	2

## SCILLITOXIN

7	70	70	30	3
8	80	60	40	3
9	70+50+50	60	40	7
10	70+50+50	35	65	7
11	50+50+50†			
12	50+50+50	22	78	3

## FLONAMUS

7	50	102	— 2	1
8	50	87	13	1
9	50×2	54	46	2
10	50×2	44	56	2

## ADONIDIN

8	58+58 <sub>1</sub>			
9	58+58+58	42	58	3
10	80+60	27	73	4

†Suddenly fatal

The experiments furnish the following averages

Crystalline ouabain, initial dose, 76 per cent of fatal, persistence of action after an interval of one day equal to 24 per cent of the fatal  
 scillophanthus initial dose, 68 per cent of fatal, persistence of action after an interval of one day equal to 25 per cent of the fatal

In several of the experiments in Table 6 the animals received more than one initial dose, in such cases these were given on successive days except in the case of scillitoxin, in which the initial doses were given at intervals of two days. In all cases the interval before the final test is reckoned from the date of the first initial dose

German digitalin is said to consist of digitonin to a very large extent and the action of digitonin on the heart is not quite like that of true digitalin, so that it is not surprising that the results obtained with this preparation are not very satisfactory. The similarity of action to that of digitalein is to be noted

Digitalis also contains digitonin, but the amount present in the leaf is said to be small, and it should be remembered that the cardiac action

of digitonin is not obtained after the oral administration of digitalis or the other digitalins. The final test was made with the same drug which was used for the initial dose in every experiment recorded in Table 6 but we had found that all of these digitalis bodies are synergists of ouabain.

The digitonin was administered intramuscularly in Experiments 1 to 9 inclusive, and intravenously in the others.

TABLE 7—PERSISTENCE OF DIGITONIN ACTION IN DOGS

Experiment	Initial Dose Per Cent of Fatal	Dose Required After Interval	Persistence of Action Per Cent of Fatal	Interval in Days
1	95	60	40	3
2	60	100	00	11
4	95	100	00	2
5	80	75	25	9
7	95	100	00	5
9	95	100	00	9
10	95	77	23	1
11	95	67	33	1
12	80	100	00	3
13	95	100	00	3

TABLE 8—DIGITALIS IN REPEATED DOSES TO RABBITS INTRAVENOUSLY

(Doses in milligrams per kilogram of body-weight)

Experi	DAYS											Total
	1	2	3	4	5	6	7	8	9	10	11	
1	50	67		100	100		200		200		300	1,017
2	100		100	100		200		200		200	250	1,150
3	165		200		200		200	250	200			1,215
4	160		200				250	250	200	350	300	1,710
5	170		200		200		200	250	250	500	300	2,070
6	200	200										400
7	200	200										400
8	200					250	250					700
9	200			200		200	250					850
10	200					200	250					650
11	400											400

\* Fatal    † Two doses at intervals of three hours, fatal

It is evident that dogs do not usually show persistence of digitonin action for long periods, and of the eight experiments in which the duration of the interval was more than a day, only two, (1 and 5,) show any persistence of action. That the action did actually persist in these two cases is rendered more probable by the fact that the first of these animals, which shows persistence of action amounting to 40 per cent of the fatal after three days, was greatly depressed for two days following the first dose, and the other animal which shows persistence of action equal to 25

per cent of the fatal, had lost 1.5 kg of body-weight during the interval. The weight at the time of the first injection was 12.5 kg, and at the time of the final test the weight was 11 kg.

Here again the attention is attracted by the question whether individual differences in tolerance and susceptibility stand in any sort of relation to differences in the individual capacity for elimination as suggested in the discussion of Table 1.

In the fourth and fifth experiments the animals received two doses each on the tenth day. Two hundred and fifty mg of digitalis per kg of body-weight appears to be the average fatal intravenous dose for the rabbit, but two rabbits survived doses of 300 mg per kg each, and one of these No. 5, had had two doses of 250 mg per kg each on the previous day.

TABLE 9.—EFFECT OF DIGITOXIN IN REPEATED DOSES TO RABBITS BY VEIN  
(Doses are given in milligrams per kilogram of weight)

Experi	DAYS								Total
	1	2	3	4	5	6	7	8	
1	0.75		0.5	0.75					2.0
2	0.5	0.5	0.5	0.5		0.5	0.75		3.25
3	0.5		0.5	0.5		0.5	0.75		*2.75
4	0.75		1.5	1.5					*3.75
5	0.5		0.75	0.75		0.75	0.75		3.5
6	0.75	0.75	0.75		0.75	0.75			3.75
7	0.5	0.75	0.75		0.75	0.75	0.75	0.75	5.0

\* Fatal, 1.0 milligram on tenth day and 1.0 mg on twelfth day.

The eleven rabbits weighed 18.41 kg; they received a total of 19,000 mg of digitalis during a total of seventy days of experimentation or an average of less than a week for each animal, but even this stupendous amount does not represent the limits of dosage for this animal, but its capacity for eliminating the digitalins was not suspected at the time the experiments were conducted.

In this connection it must be remembered that the amounts administered to these rabbits correspond to very much larger amounts administered by the stomach, or subcutaneously.

The fourth animal of this series died of respiratory failure. The seven rabbits received an average total of more than 3.5 mg of digitoxin per kg during the entire period.

Impressive as the figures for this and the preceding table are, they lose much of their significance in view of the results recorded in Table 10, in which it is shown that the rabbit eliminates digitoxin with surprising rapidity.

The following is the protocol of an experiment which shows that the rabbit exhibits no persistence of action of digitoxin after an interval of a few hours following the intravenous administration of a nearly fatal dose.

May 29, 1912 Rabbit, weight, 1.7 kg  
 8 41 a m 1.0 mg digitoxin per kg by vein, some depression  
 9 41 a m Animal sitting up  
 12 56 p m 1.0 mg digitoxin per kg as before  
 1 10 p m Effects about the same as after previous dose  
 1 56 p m Appears to be nearly normal  
 2 56 p m Ouabain, slow and continuous injection by vein  
 3 34 p m Death after injection of 0.19 mg ouabain per kg, on the full fatal dose of ouabain

TABLE 10—PERSISTENCE OF ACTION OF DIGITOXIN IN THE RABBIT

(Doses in mg per kg of body-weight)

Initial Dose of Digitoxin	Dose Required After Interval	Interval in Hours	Persistence of Action
4.0 (subcut )	0.206 ouabain	26	00
0.75 (vein)	0.245 ouabain	4.5	00
0.75 (vein)	0.212 ouabain	4.5	00
2.0 (vein)	0.19 ouabain	*	00

\* See protocol

I believe that hitherto no one has suspected that the rabbit is capable of eliminating digitalis and digitoxin with the extraordinary rapidity indicated in Tables 8, 9 and 10, and as shown in the protocol of the experiment. Certainly no one has ever before recorded the administration of digitoxin in such amounts and at such short intervals during studies of this nature, for it must be remembered that the subcutaneous and oral administration are in no way comparable to the intravenous injection of this principle, because of the slow and uncertain absorption from the gastro-intestinal tract and from the subcutaneous tissues of the rabbit (See Experiment 1, Table 10.)

It is hardly necessary, therefore, to call attention to the fact that previous studies of cumulation, so-called, based on the oral or subcutaneous administration of the digitalins to rabbits lose much of their value because it is obvious that absorption is a more important factor in the results so obtained than is the persistence of action which follows the absorption into the blood-stream of the drugs so administered.

It will be understood that the doses given in Table 11 apply only to the specimens of the drugs used by us in these experiments, but crystalline ouabain appears to be of constant composition and activity.

The fluid extracts used were obtained from a reputable firm, but it is probable that they do not represent the full activity of the drugs from which they were prepared. The tincture of digitalis used was prepared in this laboratory, care being taken to insure the complete exhaustion of the drug.

TABLE 11—FATAL DOSES OF DIGITALINS BY VEIN IN MILLIGRAMS PER KILO  
GRAM OF BODY-WEIGHT

CAT		
Ouabain (crystalline strophanthin, so called)		0 1
Digitoxin (specimen used in Series 1, Table 2)		0 3
Digitoxin (specimen used in Series 2, Table 2)		0 5
Scillitoxin		0 4
Digitalin (true)		1 5
Helleborein		1 7
Convallamarin		1 7
Digitalein		3 5
Digitalin, German		3 6
Adonidin		4 35
Convallaria (fluid extract used)		50 0
Apocynum (fluid extract used)		70 0
Digitalis (tincture prepared by ourselves)		100 00
Black hellebore (fluid extract)		100 00
Euonymus (fluid extract)		475 0
Squill (fluid extract used)		575 0
DOG		
Ouabain	0 125 to	0 175
Digitoxin (specimen used in Series 1, Table 2)		0 5
Digitalis		125 0
RABBIT *		
Ouabain		0 2
Digitoxin (specimen used in Series 1, Table 2)	0 75 to	1 0
Digitoxin (specimen used in Series 2, Table 2)	1 0 to	1 5
Digitalis	200 0 to	250 0

\* The doses given are for rabbits weighing about 1,800 gm or less, fully grown rabbits appear to be slightly more susceptible than this to the digitalins

Reference to the table suggests some curious relationships between several of the digitalins, for example, digitoxin and scillitoxin are about equal in activity and their persistence of action is not widely different, true digitalin, helleborein and convallamarin are almost exactly alike in activity, and none of these three shows a markedly persistent action German digitalin and digitalein are about equal in activity, and we know that both of these partake of the nature of true digitalin on the one hand, and of digitonin on the other <sup>10</sup>

Too much stress should not be placed on similarities in activity of the digitalins, however, since none of these bodies except ouabain is found in commerce in a pure form Ouabain appears to have only traces of impurities present

#### ANALYSIS OF CERTAIN RESULTS OF FRAENKEL'S

Reference has been made to the fact that Fraenkel's conclusions based on results obtained when using digitalins on the cat are irreconcilable with mine It is necessary, therefore to discuss some of his experiments

<sup>10</sup> Schmiedeberg Arch f exper Path u Pharm, 1875, iii 16

which, interpreted correctly, actually confirm my own results in all essentials, I believe

Fraenkel<sup>4</sup> fixed the fatal dose of Merck's crystalline digitoxin for the cat by subcutaneous injection at 0.08 mg per kg of body-weight and then he administered specified fractional parts of this dose daily, observing the onset and severity of the gastro-intestinal symptoms, the effects on the heart and pulse-rate and the number of such doses that the animal would survive, comparing the effects of digitoxin with those of the other digitalins in common use, including digitalin and strophanthin

TABLE 12—EFFECT OF DIGITOXIN ON CATS

(Taken from article by Fraenkel<sup>4</sup>)

Experiment	Digitoxin Given Per Kg	After How Many Days	How Many Doses Vomiting?	After How Many Doses Sick?	Remarks
40	22 x 0.02	5	Not seen	Not seen	Remained sound
9	9 x 0.03	2	3	9	Stopped, Animal very sick
20	2 x 0.04	2	Not seen	Not seen	Remained sound
44	16 x 0.04	4	6	6	Death after 16 doses
11	5 x 0.041	3	5	5	Stopped after 5 doses, very sick
8	7 x 0.05	3-4	3-4	4	Death after 7 doses
10	7 x 0.087	1	2	3	Death after 7 doses

It will be seen by reference to Table 12, which is taken from Fraenkel's article, that several of his cats survived a total of much more than the amount which Fraenkel gives as the single fatal dose, thus, one of his animals is stated to have received sixteen daily doses, each of which was 50 per cent of the fatal, or a total amount equal to eight times the single fatal dose within a period of fifteen days, another survived three times the fatal single dose, administered in five days, while two required to cause death amounts equal to four and seven, times the fatal dose, respectively, within a period of a week

If these conclusions were correct it would show that the action of digitoxin is not very persistent when used in that way, but while Fraenkel does not state specifically the number of experiments which he made to determine the toxicity of digitoxin for the cat, he gives the protocol of only one experiment and in that the animal died on the tenth day after the injection

No less than five observers working independently in this laboratory at different times have been unable to confirm Fraenkel's determination of the fatal dose of digitoxin for the cat

Bailey, Brody, Eggleston, Mr M I Smith (one of my students), and I have found that the fatal dose of different samples of Merck's crystalline digitoxin is much larger than that given by Fraenkel



Bailey found that doses of 0.1 mg, and 0.2 mg, per kg of body-weight injected subcutaneously, produced very little effect on the pulse-rate of the cat, and, in fact, little or no perceptible effect of any sort was produced by these doses administered to two animals.

Hatcher and Brody,<sup>9</sup> Eggleston, and later I, while repeating the work, have found that the fatal intravenous dose of several different samples of Merck's crystalline digitoxin for the cat is approximately 0.3 mg to 0.35 mg per kg of body-weight, and I have found the fatal dose for the cat by subcutaneous injection to be somewhat larger than that by vein, as one might expect. I have quite recently found a specimen of Merck's digitoxin obtained from another firm, and not bearing Merck's label, to have only about 60 per cent of the activity of the specimens previously examined. (This is the weaker specimen mentioned in Table 11.)

If we accept 0.4 mg of digitoxin per kg of body-weight as the average fatal dose for the cat by subcutaneous injection, it will be seen that Fraenkel's results, so far from being irreconcilable with my own, afford strong corroborative evidence of the persistence of action in the cat.

If the fatal dose of digitoxin used by Fraenkel was really 0.4 mg per kg when administered subcutaneously, his animals received only a little more than the single fatal dose within a period of a week, and instead of receiving totals of three, four, seven and eight, times the single fatal dose, respectively, they received totals of three-fifths (this animal survived), one, one and a half, and one and three-fifths times the single fatal dose, from which the last three died.

One might argue that the specimen of Merck's crystalline digitoxin used by Fraenkel was far more active than the specimens used in this laboratory, and I am well aware that it is commonly stated that the activity of different specimens of all of the digitalis principles varies widely, but while the activity of a given principle made by different manufacturers may show great variations, and the product made at different times by the same manufacturer may vary somewhat, the results obtained by numerous observers indicate no very great variation in the activity of Merck's crystalline digitoxin.

Among those who have determined the activity of digitoxin and whose results are in fair agreement with those obtained in this laboratory (allowance being made for differences due to different methods of testing), are Lyons and Famulener,<sup>11</sup> Worth Hale<sup>12</sup> and Koppe.<sup>13</sup> On the other hand, I know of no one whose results confirm those of Fraenkel.

<sup>11</sup> Lyons and Famulener. *Proc Am Pharm Assn*, 1902, 1, 424.

<sup>12</sup> Hale, Worth. *Bull* 74, 1911, Hyg Lab, U S Public Health and Marine Hospital Service.

<sup>13</sup> Koppe. *Arch f exper Path u Pharmacol*, 1875, iii, 274.

If the digitoxin used by Fraenkel behaved in the way indicated by him it means that the specimen of Merck's digitoxin employed by him is far more active than any which has been used in experimentation in this country, and furthermore, that its behavior is much more like that of ouabain, so far as persistence of action is concerned, than like that of digitalis

No other worker either in Europe or America has ever reported such activity for digitoxin on mammals as Fraenkel has reported in this series of experiments, so far as I am aware, and I believe that Fraenkel's results with repeated injections disprove his own statement as to the lethal dose of this drug, if by lethal dose we are to understand the amount which will kill at least half of the animals in a series through the action on the heart

There is little doubt that when an animal is made ill by the injection of one of the digitalins it is more apt to succumb to more or less accidental conditions during a prolonged confinement than is a normal animal, and I believe it to be wholly erroneous to attribute all the deaths which occur in ten days or more after the administration of a single dose of the digitalins to the cardiac action of the drug

It might be urged that digitoxin behaves differently after subcutaneous and intravenous injections, I have, therefore, repeated Fraenkel's experiments to the extent of injecting repeated doses of less than 50 per cent of the fatal dose subcutaneously. In these experiments the cats received 0.6 mg per kg of body-weight in four days, 0.75 mg per kg in five days, and 0.7 mg per kg in three injections in six days, before death resulted. These results agree very well with those reported by Fraenkel so far as the actual amounts administered are concerned. I am therefore forced to the conclusion that the so-called fatal dose of digitoxin as determined by Fraenkel, can be fatal only under very exceptional conditions, and is of no value whatever in determining the persistence of action of digitoxin.

This misconception of the activity of digitoxin appears to have led Fraenkel into another error. He concluded that the interval of time which must elapse after a digitalis principle enters the circulation before its action on the heart is induced must be proportional to the chemical affinity existing between the drug and the tissue on which it acts, whereas the duration of the action must depend on the stability of the combination of drug and tissue.

The truth of this conclusion, based on theoretical considerations seems self-evident, nevertheless it was based on a wholly erroneous idea, in that Fraenkel believed that the action of digitoxin on the heart was not exerted for many hours after its introduction into the blood-stream and he states that even sixty hours may elapse after the administration of

a toxic dose before this cardiac action is induced. It is obvious that he fell into this error partly because of his erroneous belief that he was administering a highly toxic dose, when, in reality, he was administering only a small part of the fatal dose.

It is perfectly true that digitoxin does not exert its full action immediately after the injection of small amounts into the circulation, but death may result in about five minutes after injection of about twice the ordinary fatal dose of digitoxin directly into the veins of the cat or dog. When a very large dose of digitoxin is injected directly into the veins the action is induced with amazing swiftness, the heart stopping suddenly almost without warning on its part.

The belief which is well nigh universal, that digitoxin is an extraordinarily toxic substance, is based mainly on the well-known experiment in which Koppe<sup>13</sup> administered to himself by the mouth three doses of digitoxin amounting altogether to 3.5 mg. in a period of five days, 2 mg. having been taken four days after the second dose of 1 mg.

Since Koppe had previously given a rabbit 4 mg. of the digitoxin subcutaneously without causing death, there is little doubt that he was extraordinarily susceptible, or that his illness following the taking of the digitoxin was due to other causes in part.

#### CONCLUSIONS

In presenting the results of my experiments I would not intimate a belief that the last word had been spoken concerning the persistence of action of the digitalins or the so-called cumulation of these bodies, but I do believe that my results afford a starting point for investigating the subject anew.

It is obvious that the rabbit is not suited for these studies and that the cat serves the purpose better than the dog. The injection of the digitalins directly into the circulation affords so much greater accuracy of observation than the oral and subcutaneous routes, that the former method alone should be used for these investigations.

Changes in the heart-rate of the cat and the rabbit occur so often independently of the administration of the digitalins that they afford very little information concerning the persistence of action of these drugs.

The several digitalins vary widely in their toxicity for any given species of animal, and the different species of animals show enormous differences in susceptibility to a given digitalin, but so far as I have been able to determine, as the result of a large number of experiments, the various digitalins maintain their relative positions in order of toxicity, regardless of the animal used for the determination provided that the drug is introduced directly into the circulation, but the absorption of these bodies from the gastro-intestinal tract is so variable that the effects

which follow the oral administration afford no clue to the activity which they will exert when they are injected directly into the circulation

It remains for the clinician to determine whether it will be advantageous in a given condition to utilize the prolonged actions of digitalis and digitoxin or the briefer actions of strophanthus and digitalin, but it seems more than probable that the more persistent action will be found preferable in certain chronic cardiac conditions, whereas the less lasting digitalin action probably will be preferred in certain conditions such as acute cardiac dilatation

It is of the first importance to the clinician to know that the various digitalins are synergistic in their action, and that when one member of the group is used in such a way that its action is elicited promptly (as after intramuscular, or intravenous injection) during the period when the action of a previously used digitalin persists, the dose of the drug so used must be regulated carefully because inattention to this detail may result disastrously

#### SUMMARY

The production of the phenomena commonly called "cumulation" of the digitalins, depends on the relationships existing among a number of factors, including absorption, elimination and persistence of action, all of which are in need of investigation. The use of the term cumulation tends to perpetuate a misconception

The actions of the digitalins persist for periods of time which vary widely with the different members of the group, and with the species of animal employed

The actions of digitoxin and digitalis persist longer than do those of the other digitalins in common use

The cat shows this persistence of digitalis action much longer than the dog, rabbit or white rat

The cardiac actions of a single very large intravenous dose of digitalis or digitoxin may persist for a full month in the cat, but for only a few hours in the rabbit

The actions of the largest sublethal dose of digitalin, ouabain or strophanthus persist for only a day, or at most, a few days, in the cat

It remains for the clinician to determine whether the long-lasting action of digitalis or the briefer action of strophanthus is to be preferred in a given condition of cardiac disease, but strophanthus cannot rival digitalis in general use until we learn more of the conditions governing its absorption from the gastro-intestinal tract, and of this we know practically nothing at present

Careful regulation of the therapeutic dosage of the digitalins is necessary in order to avoid accidents. This is especially necessary when they are used in such a way that the action is elicited promptly during

the period when the action of a previously used digitalin persists, and in this connection it must be remembered that every digitalin is a synergist of every other member of the group

All of the digitalins maintain their relative position with regard to activity, so far as we have tested them on different mammals, by intra-venous injection, and digitoxin has never been found by any observer to be as active as crystalline ouabain when tested on mammals in this way, hence there is no sufficient reason for the wide-spread belief that digitoxin is enormously toxic for man, as compared with other digitalins

No fixed ratio of activity can be determined for the digitalins when they are administered orally, because of great differences in the rate of absorption from the gastro-intestinal tract

The full effects of moderately large doses of digitoxin are not exerted on the heart at once even when they are administered intravenously, but severe symptoms of poisoning may be elicited in a few seconds, and death may occur within two minutes, after the intravenous injection of a very large dose of digitoxin

The rabbit eliminates certain of the digitalins, at least, with a rapidity hitherto unsuspected, and previous studies of the so-called cumulative actions of these bodies, in which they were administered orally, or subcutaneously to rabbits, lead to wholly erroneous conclusions

Changes in the pulse-rate amounting to fifty beats per minute occur spontaneously in the cat and the rabbit, and large doses of digitalis often fail to elicit any constant changes in the pulse-rate of these animals, hence such changes as may occur after the administration of the digitalins to these animals afford no trustworthy indication of the persistence of action of the digitalins (See protocol of experiment, p 273 )

Further studies of the digitalins are in progress in this laboratory, among the problems under investigation being those of absorption from the gastro-intestinal tract, the rate at which the digitalins leave the blood-stream, their elimination from the organism, their storage in the tissues, and their persistence of action

I wish to acknowledge my indebtedness to Mr M I Smith, one of my students, for assistance in carrying out many of the experiments in this research

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## THE FAT METABOLISM OF LIPOMAS

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CHICAGO

There is a widespread belief that the fats of lipomas are not available to the host as a source of reserve food-supply. This is based on certain reputed instances in which the bearer of a lipoma is said to have become greatly emaciated from some intercurrent disease, notwithstanding which the lipoma has either remained its original size or has even continued to grow. Specific cases in which such occurrences have been accurately observed and reported are, however, difficult to find.

Shattock,<sup>1</sup> in an interesting discussion of "Localized Fatty Deposits," has commented on this paucity of evidence. He himself knew of but two such reputed cases, and reinvestigation of some of the supposed lipomas in one of these cases showed them to be caseous lymph-nodes. Furthermore, he mentions a third case in which a subcutaneous lipoma *did* decrease in size during the emaciation of the patient. A diligent search of the literature has not revealed to me many positive observations on this point.

Askanazy<sup>2</sup> reports the presence of multiple lipomas (which he looks on as a replacement of lymph-nodes by fat, comparable to the normal involution of the thymus) in a woman who became emaciated because of a thyroid sarcoma, but he does not state whether the lipomas grew or diminished in size during the emaciation. Under the caption of "Subperitoneal Lipomata," Campbell<sup>3</sup> reports a case in which the tumor increased in size during the progress of emaciation, but the tumor was in reality a fatty sarcoma, and hence falls outside the limits of this problem. Adam<sup>4</sup> also states that in the huge retroperitoneal lipomas it is noticeable that the mass continues to grow and to enlarge at the expense of the rest of the body, while the normal fat deposits are being exhausted by the emaciating patient. This feature seems prominent in

<sup>1</sup> From the Pathological Laboratory of the University of Chicago

<sup>\*</sup> Submitted for publication July 18, 1912

<sup>1</sup> Shattock. Proc. Royal Soc. Med., 1909, II, 176

<sup>2</sup> Askanazy. Virchow's Arch. f. path. Anat., 1899, clviii, 408

<sup>3</sup> Campbell. Brit. Med. Jour., Nov. 28, 1903, p. 1397

<sup>4</sup> Adam. Montreal Med. Jour., 1897, xxv, 529 and 620

most of the fatty tumors which arise in the retroperitoneal region as is brought out in the compilation of eighty-one cases by Voeckler,<sup>5</sup> most of which showed cachexia

The nature of these tumors is somewhat uncertain—they are more cellular than ordinary lipomas, have a great tendency to myxomatous change, and resemble malignant tumors in their fatal outcome and in the tendency to recur after removal. In not a few there is an actual sarcomatous transformation of the tumor, which is especially likely to be observed in the recurrent growths, as in Voeckler's case. These tumors of the perirenal fat tissue are not exactly comparable with subcutaneous lipomas, but they do present in a conspicuous way the ability of tumors to lay up a deposit of fat which the emaciating body cannot use for its own purposes. Therefore, tumor cells can not only build up their own cellular structure of proteins which are inaccessible to the rest of the wasting body, but they can also lay on and withhold fat, which seems in all respects to resemble the normal stored food. Since normal tissues do not ordinarily store fat for their own use, but for the use of the entire organism, this holding of fat by tumor cells when the rest of the body needs it, is entirely out of harmony with normal fat metabolism and challenges explanation.

Although many of the text-books on general pathology and pathology of tumors entirely omit mention of this property of lipomas (Aschoff, Senn, Bland-Sutton, Delafield and Prudden, Beattie and Dickson American Text-Book), yet there are several which give general statements without specific references or data. Borst<sup>6</sup> states that the autonomy of lipomas is shown by the fact that when, in the course of a general emaciation, the physiologic fat depots of the body disappear, an existing lipoma will remain unaffected, or even continue to grow, further, it is also frequently observed that lipomas may develop on extremely emaciated individuals. Kaufmann<sup>7</sup> says that in general emaciation of the host, lipomas do not participate, which illustrates well the independence of the tumors. Ziegler, in his General Pathology, says, "A complete disappearance of a lipoma does not take place in the case of extreme general emaciation of the individual."

That fat in lipomas is not necessarily unavailable to the organism is shown by certain cases in which absorption of the tumors has occurred. One of these is the case previously quoted from Shattock.<sup>1</sup> Most striking is the case described by Broca.<sup>8</sup> A man, 31 years old, had a five-pound lipoma excised from the thigh. Five months later hundreds of small fatty tumors appeared all over the body, and persisted and developed

5 Voeckler *Deutsch Ztschr f Chir*, 1908, *xcix*, 149

6 Borst *Die Lehre von den Geschwulste*, 1, 137

7 Kaufmann *Spezielle Pathologie*, 1911, ed 6, p 1312

8 Quoted by Warthin, *Reference Handb Med Sc*

about forty years, until the man was nearly 70 years old. He then began to suffer from dysphagia, which caused emaciation. This at first did not affect the tumors, but after several weeks the emaciation became extreme and the tumors diminished. Death finally resulted from starvation. At autopsy no trace of fat was found in the normal fat deposits. A large fatty tumor surrounded the esophagus for the greater part of the extent, occluding the lumen. Other fatty growths were found in many places. Many of the tumors had lost their fat and consisted of fibrous tissue, the others presented the appearance of fibrolipomata. The classification of such a tumor, with sudden dissemination like a cancer, but of essentially benign course, is a difficult matter, and this uncertainty makes the true significance of this remarkable case questionable.

Baker<sup>9</sup> reports a case in which multiple cervical lipomas became reduced in size (to one-half or one-third their original size) during a period of emaciation brought about by some obscure lung disease, increasing in size again later. Unfortunately the report lacks many details necessary to carry conviction as to the fatty nature of the tumors. According to the statistics of Madelung,<sup>10</sup> the diffuse fatty tumors of the neck are characterized by independence from the general body condition. He himself observed a case in which emaciation of the patient from pulmonary disease had no effect on the growth in the neck. Of the cases in the literature collected by him, some of the patients were well nourished, none obese, some were thin or even emaciated. Of these, Kuster's case showed a cessation of growth in the lipoma when the patient became emaciated (from "gastric disorder"), but the lipoma did not diminish in size.

It is indeed difficult to understand how the fat of a lipoma can exist as it does, in intimate relation to the blood-vessels, and not be utilized when the host needs fat. We know of no anatomic peculiarity that can explain such anomalous deportment on the part of the fatty areolar tissue of lipomas. As Shattock has emphasized, the lipomas are structurally comparable to certain normal localized fat deposits, e. g., the "hump" of the dromedaries, the fat-tailed sheep, the steatopygous masses of Hottentots, etc., yet all these deposits are drawn on when needed for nutriment. The camel starts off on a journey across the desert with full and erect humps and reaches its destination with the humps reduced to pendant, flabby bags of skin. On the other hand, more comparable with the reputed behavior of lipomas, are the sucking cushions in the cheeks of infants, which persist during emaciation.

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<sup>9</sup> Baker *Tr Path Soc*, London, 1879, xxx, 417

<sup>10</sup> Madelung *Arch f klin Chir*, 1888, xxxvii, 106



## CHEMISTRY OF NORMAL AND LIPOMA FAT

A chemical difference between the lipoma fat and the fat of the normal fat depots might explain this unavailability of lipoma fat, but no such difference, of sufficient magnitude to be revealed by existing chemical methods, has been found. The careful study of lipoma fat by Jaeckle<sup>11</sup> showed a remarkably close resemblance to normal subcutaneous human fat. In the fatty masses of adiposis dolorosa Edsall<sup>12</sup> found the fat quite similar to normal fat.

Failing adequate explanation by structure or chemical composition, it might be imagined that there is a deficiency or abnormality of the enzymes of fat metabolism in the connective tissues. This possibility has not been investigated previously. According to the investigations of fat metabolism by Kastle and Loevenhart, the storage of fat by tissues depends on the presence in these tissues of the enzyme lipase, which acts reversibly, either to split fat into fatty acids or glycerin, or to synthesize fat from these diffusible constituents as they are provided by the blood, the direction of the reaction depending on the conditions of equilibrium. One might imagine that absence of lipase from lipomas might account for the inability of the fats to be rendered available to the body, however in this case the storage of the fat in the lipoma would be difficult to explain. Bearing on this hypothesis is the observation of Loevenhart,<sup>13</sup> that watery extracts which he prepared from the retroperitoneal and pericardial fat had less lipolytic activity than extracts from subcutaneous fats, and that the two former fats are absorbed less rapidly during emaciation than are the subcutaneous fats.

We have tested the lipolytic activity of a number of lipomas kindly supplied us by surgical friends, and also specimens of human fat tissue. At first attempts were made to observe autolipolysis of the fatty tissues, by contrasting the development of acids in fresh fatty tissue or lipomas with boiled portions of the same specimens. These experiments all failed, because the antiseptics (toluene, chloroform) are taken up to such an extent by the fats that putrefaction occurs even in the presence of a large amount of antiseptic. We therefore were obliged to remove the fat by extracting the tissue with ether as rapidly as possible until free from fat, then grinding and drying the extracted residue, which could then be kept until wanted. We have no means of knowing to how great an extent, if any, the lipase is injured by this proceeding, but it is not destroyed. Such extracted tissues when added to natural fats and simpler esters in watery solutions or emulsion cause marked hydrolysis, but any quantitative results obtained in such experiments are worthless. The

11 Jaeckle *Zeitschrift für physiol. Chem.*, 1902, **XXXVI**, 53

12 Edsall *Amer. Jour. Med. Sc.*, 1902, **CXXIV**, 994

13 Loevenhart *Am. Jour. Physiol.*, 1902, **VI**, 341

proportion of stroma, blood-vessels, fascia, etc, in such tissue, the manipulations necessary in preparing the material and the unnatural conditions under which the lipolysis is carried out, must necessarily have so much influence on the results obtained with any sample of tissue that these results cannot be considered as reflecting the lipolytic activity of this tissue in its natural condition. All we can say is that our tissues as prepared are or are not possessed of thermolabile lipolytic activity. In the experiments were used natural human fat, lipoma fat, olive oil, ethyl butyrate and triacetin. The latter glycerol ester, which is recommended by Taylor,<sup>14</sup> seems to be, as he maintains, the best for experimental study of lipolysis, because it is water soluble and yet is a triglycerid. The insoluble fats are too slowly attacked by lipase because of the small surface for action which they exhibit even when emulsionized, while such simple soluble esters as ethyl butyrate are chemically too dissimilar to the triglycerids of natural fats to make them valuable indicators of the normal lipases which split triglycerids.

#### EXPERIMENTS

The experiments were conducted as follows

One-half gram of the powdered tissue was placed in 50 c c of water to which 2 c c toluene was added, and then 2 to 4 c c of the fat or ester was added, as indicated in the tables. The various experiments were performed at different times, and through an oversight the amounts of fats and esters used were not the same in each case. This, however, is not a matter of great importance, for the results are, as previously emphasized, qualitative only and not quantitative. Phenolphthalein was used as the indicator, and titration was made with  $n/10$  NaOH and HCl, the figures given representing cubic centimeters of the  $n/10$  alkali required to neutralize. Neutralization was done at various intervals, the length of which probably has some influence on the total results, for it is evident from the data given that with each tissue the amount of acid formed is not very different whether the interval is one, two, or several days, suggesting that after a certain degree of acidity is reached, there begins to be an inhibition of the hydrolysis. With all specimens, it will be noticed, there was more hydrolysis when the tissue that had been heated in boiling water for thirty minutes was present than when there was only water, indicating that there is some thermolabile agent which accelerates hydrolysis. There is, however, in every case except that of the action of the fibrosarcoma on lipoma fat and olive oil, a definite excess of hydrolysis in the presence of unboiled tissues, whether lipomas, sarcomas or normal fat tissue. There are, however, no quantitative differences which seem striking enough to be of any significance whatever under the conditions of the experiment. Usually there is considerable more hydrolysis by boiled tissues than by water alone, but we have not sufficient data to permit of speculation as to whether this indicates a thermostable lipase, or an excess of hydrolysis by water in the presence of colloids.

The materials used were as follows

*Lipoma X*—Mixed material, obtained by removing fat from three subcutaneous lipomas from different persons

*Lipoma A*—Tissue from a single large subcutaneous lipoma

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<sup>14</sup> Taylor Jour Biol Chem, 1906, 11, 87

*Lipoma B*—Diffuse lipoma of the neck, "Madelung's Neck"—freed from fat

*Fibrosarcoma*—A large retroperitoneal tumor from a cow, extracted with ether

*Sarcoma of the Liver*—An alveolar sarcoma of the liver of a cow, not known whether primary or secondary Ether extracted

*Omental Fat Tissue*—Normal tissue from a moderately emaciated tuberculous patient, freed from fat by ether

*Perirenal Fat*—From same subject, ether extracted

*Subcutaneous Fat*—From the same subject, ether extracted

The results of the experiments are summarized in the accompanying tables 1, 2, 3 and 4

TABLE 1—TRIACETIN

Days Incubation	1	3	5	7	14	Total	Daily Aver
Water only (2 cc ester)	0 10	0 39	0 51	0 62	0 74	2 36	0 17
Lipoma X, boiled (2 cc ester)	1 53	1 96	2 77	3 21	3 14	8 45	0 60
Lipoma X, fresh (2 cc ester)	4 29	6 60	6 65	6 80	7 19	31 43	2 24
Lipoma A, boiled (2 cc ester)	1 00	1 30	1 64	2 20	2 18	8 32	0 60
Lipoma A, fresh (2 cc ester)	3 40	5 20	7 12	8 13	8 46	32 31	2 30
Lipoma B, boiled (2 cc ester)	2 80		2 80		2 72	7 32	0 52
Lipoma B, fresh (2 cc ester)	12 81		17 38		17 48	47 67	3 40
Fibrosarcoma, boiled (2 cc ester)	1 91		2 41		2 35	6 67	0 47
Fibrosarcoma, fresh (2 cc ester)	10 42		13 40		12 60	36 42	2 60
Sarcoma of liver, boiled (2 cc ester)	2 08		1 94		2 01	6 03	0 43
Sarcoma of liver, fresh (2 cc ester)	13 11		19 08		20 00	52 19	3 73
Omental fat tissue, boiled (4 cc ester)	3 45	3 90		4 59	6 45	18 39	1 31
Omental fat tissue, fresh (4 cc ester)	8 45	12 42		15 01	23 35	59 23	4 23
Perirenal fat tissue, boiled (4 cc ester)	3 20		3 90		6 40	13 50	0 96
Perirenal fat tissue, fresh (4 cc ester)	11 65		15 75		27 00	54 40	3 90
Subcutaneous fat tissue, boiled (2 cc ester)	1 98	2 01	2 71	2 50		8 30	0 83
Subcutaneous fat tissue, fresh (2 cc ester)	3 16	3 00	5 00	5 30		16 46	1 65

TABLE 2—ETHYL BUTYRATE

Days Incubation	1	3	5	7	14	Total	Daily Aver
Water only (4 cc ester)	0 14	0 19	0 10	0 27	0 31	1 01	0 07
Lipoma X, boiled (2 cc ester)	0 50	0 51	0 60	0 46	0 67	2 74	0 30
Lipoma X, fresh (2 cc ester)	2 23	3 04	3 01	2 27	4 86	15 41	1 10
Lipoma A, boiled (4 cc ester)	0 89	0 89	0 98	0 90	1 12	4 38	0 31
Lipoma A, fresh (4 cc ester)	3 66	5 11	6 81	5 00	7 42	28 00	2 00
Fibrosarcoma tissue, boiled (4 cc ester)	1 39		1 31		1 27	3 97	0 28
Fibrosarcoma, fresh (4 cc ester)	4 68		5 60		5 55	15 83	1 13
Sarcoma of liver, boiled (4 cc ester)	1 12		1 18		1 15	3 45	0 25
Sarcoma of liver, fresh (4 cc ester)	2 36		2 80		2 76	7 92	0 56
Omental tissue, boiled (4 cc ester)	1 33	1 78		2 10	1 95	7 16	0 51
Omental tissue, fresh (4 cc ester)	3 62	4 23		4 65	6 10	19 40	1 40
Perirenal fat tissue, boiled (4 cc ester)	1 55		1 43		1 87	4 85	0 35
Perirenal fat tissue, fresh (4 cc ester)	5 60		7 10		10 85	23 55	1 68

There being no significant difference between lipoma tissue and ordinary fatty areolar tissue in regard to their activity in hydrolyzing esters, it was thought well to see if the lipoma fat itself differed from

normal fat in the degree or ease with which it is hydrolyzed by tissue and pancreatic extracts. The following experiments do not indicate that lipoma fat is peculiar in respect to its hydrolysis by pancreatic lipase. Fat was obtained alike from lipomas and normal subcutaneous and omental fat tissues, by extracting the fresh tissues in the cold with ether and removing the ether at low temperature. In two experiments 5 c c

TABLE 3—LIPOMA FAT

Days Incubation	1	3	5	7	14	Total	Daily Aver
Water alone (2 c c fat)	0 07	0 08	0 17	0 15	0 20	0 67	0 05
Lipoma A, boiled (2 c c fat)	0 17	0 42	0 60	0 53	0 72	2 44	0 17
Lipoma A, fresh (2 c c fat)	0 27	0 46	0 64	0 42	0 68	2 47	0 17
Lipoma B, boiled (2 c c fat)	1 20		1 10		0 87	3 17	0 23
Lipoma B, fresh (2 c c fat)	1 53		1 45		1 06	4 04	0 29
Fibrosarcoma, boiled (2 c c fat)	0 57		0 51		0 42	1 50	0 11
Fibrosarcoma, fresh (2 c c fat)	0 51		0 58		0 40	1 49	0 11
Sarcoma of liver, boiled (2 c c fat)	0 37		0 12		0 32	0 81	0 06
Sarcoma of liver, fresh (2 c c fat)	1 23		1 20		0 65	3 08	0 22
Omental tissue, boiled (4 c c fat)	0 60	0 60		1 33	1 50	4 03	0 29
Omental tissue, fresh (4 c c fat)	1 50	1 22		1 76	1 74	6 22	0 44
Perirenal fat, boiled (4 c c fat)	0 83		1 0		1 42	2 25	0 16
Perirenal fat, fresh (4 c c fat)	0 82		2 0		1 89	5 71	0 41

TABLE 4—OLIVE OIL

Days Incubation	1	3	5	7	14	Total	Daily Aver
Water alone (2 c c oil)	0 06	0 0	0 1	0 0	0 1	0 26	0 02
Water alone (2 c c oil)	0 0	0 0	0 0	0 0	0 09	0 09	0 01
Boiled lipoma tissue X (2 c c oil)	0 05	0 03	0 14	0 13	0 20	0 55	0 04
Fresh lipoma tissue X (2 c c oil)	0 61	0 32	0 22	0 17	0 25	1 57	0 11
Boiled lipoma tissue A (2 c c oil)	0 0	0 0	0 0	0 14	0 10	0 24	0 02
Fresh lipoma tissue A (2 c c oil)	0 17	0 28	0 24	0 36	0 42	1 47	0 11
Boiled fibrosarcoma (2 c c oil)	0 30		0 13		0 05	0 48	0 03
Fresh fibrosarcoma (2 c c oil)	0 40		0 15		0 07	0 52	0 04
Sarcoma of liver, boiled (2 c c oil)	0 23		0 07		0 27	0 57	0 04
Sarcoma of liver, fresh (2 c c oil)	1 36		0 58		0 58	2 52	0 18
Omental tissue, boiled (4 c c oil)	0 0		0 0	*	*	?	?
Omental tissue, fresh (4 c c oil)	1 12	0 47		1 70	0 87	4 16	0 30
Perirenal fat, boiled (3 c c oil)	0 15	0 20			0 56	0 91	0 06
Perirenal fat, fresh (3 c c oil)	1 75	1 00			2 56	5 31	0 38

\*Infected

lipoma fat and 5 c c normal fat were each acted on by 50 c c of a 10 per cent emulsion of fresh dog pancreas. The mixture was first neutralized to phenolphthalein, then after six days in the incubator (with toluene) the watery emulsion was approximately neutralized with  $n/10$  NaOH. After further incubation for two weeks in Experiment B, and three weeks in Experiment A, the emulsions were shaken out with equal volumes of

ether which had been neutralized to phenolphthalein, and the ethereal extracts washed by shaking out with water. The resulting ethereal extract was titrated with  $n/10$  alcoholic NaOH, and the results were found to agree with each other as closely as could be expected with the materials and methods — as shown in Table 5

TABLE 5—COMPARISON OF THE HYDROLYSIS OF LIPOMA FAT AND NORMAL FAT

	Lipoma Fat	Normal Fat
A Titration in $H_2O$ sol, 5 days	87.5	90.8
B Titration in $H_2O$ sol, 5 days,	64.8	59.4
A Titration in ether sol, 3 weeks	30.3	36.15
B Titration in ether sol, 2 weeks	19.1	22.3

## SUMMARY

The literature lacks satisfactory evidence to establish the generally accepted statement that simple subcutaneous lipomas do not give up their fat to the body during emaciation, although there are certain more or less incomplete observations in support of this contention, and also definite cases which are entirely at variance with it, there is no question that it is correct for fatty sarcomas. All reported analyses indicate that the fats of lipomas are identical with the fats of normal fat deposits. A series of experiments has also failed to indicate any lack of ability on the part of lipoma tissue to hydrolyze various fats and esters which are also hydrolyzed by normal fatty areolar tissues. No reliable method could be devised which would indicate whether lipomas and normal fat tissues differ in their quantitative action on fats and esters. Lipoma fat is hydrolyzed by pancreatic lipase as readily as is normal human adipose tissue.

# THE UTILIZATION OF PARENTERALLY INTRODUCED SERUM <sup>1</sup>

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The question as to how completely foreign proteins introduced parenterally can be utilized by the animal organism is one that has been under discussion and investigation for more than forty years. The earliest method of attack was that of injecting a protein, such as egg-white or foreign blood-serum and testing the urine for coagulable protein, on the assumption that if the protein could not be utilized by the body it would be eliminated promptly in the urine in coagulable form. If, therefore, no coagulable protein was found after such injection the protein was supposed to have been utilized by the body. Stokvis,<sup>1</sup> Ponfick,<sup>2</sup> Ott<sup>3</sup> and Lihlenfeld<sup>4</sup> have reported experiments of this type and have found that in the dog and the rabbit the injection of egg albumin is followed by albuminuria while injection of blood-serum is not. Other proteins of animal or vegetable origin likewise varied in their power to produce albuminuria.

With the development of the precipitin reaction a new method of approaching this problem was at hand. Hamburger<sup>5</sup> studied the results of the subcutaneous injection of egg-white into the rabbit and found that the serum of the rabbit ceased within about a day to show the presence of egg-albumin by the precipitin test. He also noted that on repeated injections of egg-white into the rabbit, it in time ceases to react by the

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\*From the John Herr Musser Department of Research Medicine, University of Pennsylvania, aided by a grant from the Committee on Scientific Investigation of the American Medical Association.

1 Stokvis, B. J. Hühner-Eiweiss u. Serum-eiweiss u. ihr Verhalten z. tierisch. Organismus. *Zentralbl. f. d. med. Wissensch.*, 1864, 11, 596.

2 Ponfick. Exper. Beiträge z. Lehre v. d. Transfusion. *Arch. f. path. Anat. u. Phys. u. f. klin. Med.*, 1875, LXII, 273.

3 v. Ott. Ueber den Einfluss d. Kochsalzinfusion auf d. verbluteten Organismus im Vergleich m. anderen z. Transfusion verwendeten Flüssigkeiten. *Arch. f. path. Anat. u. Phys. u. f. klin. Med.*, 1883, XCIII, 114.

4 Lihlenfeld. *Ztschr. f. phys. u. diät. Therap.*, 1899. Quoted by Lommel, See Note 11.

5 Hamburger, F. Zur Frage d. Immunisierung z. g. Eiweiss. *Wien klin. Wchnschr.*, 1902, xiv, 1188. *Arteigenheit u. Assimilation*, Leipzig-Wien, 1903. Hamburger, F., and v. Reuss, A. Die Folgen parenteraler Injektion v. verschieden genuinen Eiweisskörpern. *Wien klin. Wchnschr.*, 1904, xvii, 859.

development of albuminuria Michaelis and Oppenheimer<sup>6</sup> observed the same fact and noted that about the time the albuminuria ceases to follow the injection, the rabbit's serum contains a specific precipitin against egg-albumen. They advanced the hypothesis, therefore, that the precipitin is a denaturing agent which takes part in breaking down the foreign protein. This explanation cannot be applied to all animals, for Hamburger found that the dog is incapable of developing precipitins to foreign protein, as did also Friedenwald and Isaac.<sup>7</sup> Hamburger and Moro<sup>8</sup> have studied in man and the rabbit the time during which horse-serum could be demonstrated in the blood after subcutaneous injection. In three children they found, by the precipitin test, horse-serum (antitoxin) in the circulating blood for nineteen to thirty-one days after injection, and in each instance there developed in the child's serum, two to three days before the disappearance of the horse-protein from the blood, a specific precipitin against horse-serum. In the rabbit the horse-protein was demonstrable by the precipitin test for eight days, regardless of whether a large or a small injection had been given, and a specific precipitin against horse-serum developed in the rabbit's blood between the sixth and eighth days.

Later Hamburger and Sluka<sup>9</sup> studied, both by the precipitin test and by determining the antitoxic activity, the persistence of tetanus antitoxin (horse-serum) in the dog, goat and cat, after subcutaneous injection. By both methods they found a persistence of the foreign protein in almost undiminished quantity for five to seven days, at which time, however, a sudden, rapid diminution in the quantity occurred. To explain this entire group of findings with the precipitin test, Hamburger has advanced the hypothesis that the horse-serum is distributed in the circulating blood, neither utilized nor excreted, until the body, after a latent period, develops the power of breaking up the foreign protein.

Friedenwald and Isaac,<sup>7</sup> however, have found evidence that the substance essential to the precipitin reaction and stimulating the formation of a specific precipitin in the host is not identical with the whole protein injected and that the persistence of this essential substance cannot be taken as evidence of the persistence of the whole protein. They have injected horse-serum into both fasting dogs and dogs on a nitrogen

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6 Michaelis, L., and Oppenheimer, C. Ueber Immunität gegen Eiweisskörper, *Arch f Physiol* (Engelmann), 1902, Suppl., 336, Oppenheimer, C. Ueber d Schicksal d mit Umgehung d Darmkanals eingeführten Eiweissstoffe, *Hofmeister's Beiträge z chem Phys u Path*, 1904, iv, 263.

7 Friedenwald, U., and Isaac, S. Weitere Untersuch u d parenteral Eiweissstoffwechsel *Ztschr f exper Path u Therap*, 1907, iv, 830.

8 Hamburger, F., and Moro, E. Ueber d biolog nachweisbar Veränderung d menschlich Blut nach d Seruminjektion *Wien klin Wchnschr*, 1903, xvi, 445.

9 Hamburger, F., and Sluka, E. Ueber d Verdauungsfähigkeit d Körperzellen, *Wien klin Wchnschr*, 1905, xviii, 1323.

balance, and have studied the elimination of nitrogen in the urine, and also, by the use of the precipitin test and the complement deviation method, have studied the persistence of the foreign protein in the serum. Their chemical studies were made, with one exception, after subcutaneous injection, the biological studies, after intravenous injection. While their studies by the precipitin method confirm Hamburger's work, they find by the complement deviation method a gradual diminution of the foreign protein in the blood, beginning in the first twenty hours and continuing for eight to ten days. Moreover, in their studies of the urine, they observed almost always within the first forty-eight hours a quantitative elimination of the nitrogen injected. This result will be discussed later.

Studies based on the nitrogen elimination in the urine have been of two types (1) those on fasting animals, (2) those on animals in nitrogen equilibrium. We will consider these separately.

#### EXPERIMENTS ON FASTING ANIMALS

Forster<sup>10</sup> reports that after injecting both egg-white and horse-serum into fasting dogs an increased output of urea occurs. Lommel<sup>11</sup> in a series of investigations on seven fasting dogs recovered from 50 to 100 per cent of the nitrogen (1.5 gm) of swine-serum introduced intravenously, and most of this within six to twelve hours. Friedenwald and Isaac injected dog-, horse- and goat-serum and egg-albumen subcutaneously into dogs that had fasted from eleven to fourteen days. In all the experiments they found an increased output of nitrogen approximating the amount introduced. They quote also a personal communication from Loewy. He studied the nitrogen elimination of a fasting dog for three days before and three days after a transfusion of blood containing about 3 gm of nitrogen (amount of blood determined by change in weight of donor) and noted after transfusion an increased elimination of 1.48 gm. In all these experiments there was a definite increase of nitrogen elimination following the nitrogen injection. An experiment of Michaelis and Rona<sup>12</sup> gave a different result. They studied a fasting dog for five days before and seven days after a subcutaneous injection of 100 cc of dog-serum, containing 1.15 gm. nitrogen, and obtained no increase in the output of nitrogen. The value of their results, as well as those of Friedenwald and Isaac, is greatly diminished by the fact that their injections were made subcutaneously instead of intravenously.

<sup>10</sup> Forster *Ztschr f Biol*, 1875, xi, 496. Quoted by Friedenwald and Isaac, Note 7.

<sup>11</sup> Lommel, F. *Ueber d Eiweissabbau b parenteral Eiweisszufuhr*. *Arch f exper Path u Pharm*, 1907, lviii, 50.

<sup>12</sup> Michaelis, L. and Rona, P. *Untersuch uber d parenteral Eiweissstoffwechsel*. *Arch f d ges Physiol*, 1908, cxviii, 406.



## EXPERIMENTS ON ANIMALS IN NITROGEN EQUILIBRIUM

Lommel brought four dogs into nitrogen equilibrium. Into three he introduced dog-serum intravenously, the fourth received blood by transfusion. In none of these experiments did he find an increase in the nitrogen elimination, but when heated serum was injected he obtained promptly a quantitative elimination of the nitrogen injected. Friedenwald and Isaac, on the other hand, placed a twelve-kilo dog on a daily diet of 120 gm horse flesh and 50 gm bacon. They then injected, subcutaneously, 160 cc of dog-serum containing 1.37 gm nitrogen and during the following four days obtained an elimination of 1.51 gm of nitrogen in excess of the nitrogen of the diet.

It will be seen that the results obtained by these investigators are far from uniform.

An experiment which is a combination of the feeding and fasting methods is the following. Carter<sup>13</sup> fed a dog by mouth until it was in nitrogen equilibrium, and then ceased feeding by this method and gave for thirteen days hypodermic injections of peptonized skimmed milk and glucose. He concluded as the result of these observations that it is possible by this method to keep a dog, at least for a short time, in nitrogen equilibrium. His animal, however, received during the thirteen days of the injection period, quantities of glucose varying from 32 calories per kilo to 9 calories per kilo daily—always a quantity below the animal's caloric needs. Still more objectionable, however, is the fact that apparently more carbohydrates were given on those days on which more nitrogen was given and as undoubtedly an increase in the supply of carbohydrates tends to reduce the nitrogen catabolism the experiment is not entirely conclusive.

The irregularity in the results obtained by different observers both in fasting animals and those on nitrogen balance is, we think, explicable, and on the basis of our explanation we consider neither method suitable to the study of the question in hand. A fasting animal, when its stores of glycogen and of fat have been considerably reduced, will immediately deaminate introduced protein, utilize it to supply its caloric needs and excrete the nitrogen promptly as urea. Almost all the experiments reported in the literature on fasting animals are most readily thus explained. On the other hand, it is well known that an animal in nitrogen equilibrium eliminates promptly the greater part of any additional nitrogen administered, and thus Friedenwald and Isaac's experiments in the second group may be explained. If, however, an animal be given a nitrogen-free diet, containing sufficient carbohydrate and fat adequately to meet its caloric needs, its nitrogen excretion will be reduced.

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<sup>13</sup> Carter, H. S. *Metabolism Experiments in Artificial Nutrition*. THE ARCHIVES INT. MED., 1908, 1, 335.

to a minimum representing simply the end-product of the minimal tissue catabolism. If now there is administered a nitrogenous substance which can be completely utilized for replacing this tissue waste there will be no nitrogenous residue, the cellular catabolism will not be increased and the daily excretion of nitrogen will remain unchanged, still representing the daily cellular catabolism. If, however, a nitrogenous substance is administered which cannot be utilized for rebuilding tissues, the nitrogen thus administered will be excreted as well as the nitrogen of the daily cellular catabolism and the daily nitrogen elimination will be increased by the amount of nitrogen administered. This method has been used by Michaud<sup>14</sup> for studying the extent of utilization of various proteins given by mouth and also more recently for other purposes by McCollum<sup>15</sup>. In only one experiment in the literature, so far as we can determine, has the question of utilization of parenterally introduced protein been approached by this method. This is one of the experiments of Friedenwald and Isaac in which they placed a dog on a nitrogen poor (potato) diet and then injected egg-albumin. In this experiment only a slight increase in the nitrogen elimination followed the injection and this was referable to coagulable protein. These authors, however, have not used this method with other proteins and all their chemical studies were made after subcutaneous injections except in one experiment in which a fasting dog was given horse-serum intravenously. We therefore believed it to be worth while to again approach the problem from the chemical side, to place the animals on a suitable diet, use intravenous injections and, also, instead of giving only one injection of the protein to give injections daily for two or three successive days.

#### METHODS

Our procedure has been to place each dog on a diet of butter, rendered nitrogen-free by ether extraction, and of cane sugar in quantities sufficient to maintain a minimal nitrogen elimination without producing either diarrhea, glycosuria or vomiting. Usually this required from 70 to 85 calories per kilo. Each dog was fed daily at 5 p. m. The food was well borne and was eagerly eaten throughout the experimental periods reported. At 9 a. m. the dog was given a definite quantity of water and salt by stomach-tube and at 2 p. m. was catheterized and the twenty-four-hour urine taken. After a preliminary period of several days the nitrogen of the urine was estimated by the Kjeldahl method daily for three or four days. For the next two or three days, immediately after catheteri-

14 Michaud, L. Beitrage zur Kenntnis d. physiolog. Eiweissminimum. *Ztschr. f. physiol. Chem.*, 1909, lx, 421.

15 McCollum, E. V. Nature of the Repair Processes in Protein Metabolism, *Am. Jour. Physiol.*, 1911, xxix, 215.

zation, the animal was given intravenously each day an amount of blood-serum containing nitrogen approximately equal to that which the animal had been eliminating daily during the control period. In all other respects the régime, including the diet, was unchanged. Finally the same régime and diet and the nitrogen analyses were continued for a few days after cessation of the injections. In the early experiments the feces were collected as often as voided, which was only once in several days, and their nitrogen content estimated by the Kjeldahl method. As, however, the feces contained an amount of nitrogen equivalent to only 0.02 to 0.047 gm daily, the analysis of the feces was omitted in the later experiments. The urine was examined daily for coagulable protein by the heat and acetic acid method and for glucose by the Fehling method, and for diacetic acid by ether extraction and the ferric chlorid test.

#### AUTHOR'S EXPERIMENTS

EXPERIMENT 1—A female dog weighing 6,530 gm, was placed, on February 10, on a diet of 9 gm nitrogen free butter, 95 gm cane sugar, 500 cc water and 1 gm sodium chlorid daily. The injections of dog serum were made into a small vein of the leg under ether anesthesia. The results are shown in Table 1.

TABLE 1—NITROGEN AND COAGULABLE PROTEIN ELIMINATION IN EXPERIMENT 1

24 Hours Beginning 2 p m	Weight in Grams	Serum Injected in c c	Nitrogen of Serum in Gms	Volume of Urine in c c	Nitrogen of Urine in Gms	Coagulable Protein
Feb 14	6,640			110	96	Very faint trace
Feb 15	6,390			210	1.12	Very faint trace
Feb 16	6,455			360	1.12	Very faint trace
Feb 17	6,450	100	1.05	340	1.10	Very faint trace
Feb 18	6,460	100	1.05	280	.88	Very faint trace
Feb 19	6,240	100	1.05	230	.89	Very faint trace
Feb 20	6,280			275	.85	Very faint trace
Feb 21	6,300			290	.87	Trace

The table shows that no increase in the elimination of nitrogen during or following the period of serum injections occurred and that no significant quantity of coagulable protein appeared in the urine. Glucose and diacetic acid were not present. The conclusion is inevitable that the serum injected was completely utilized by the body for cellular anabolism.

It should perhaps be stated that the gradual fall in the nitrogen elimination is the characteristic fall that constantly occurs in an animal on a calorically adequate, nitrogen-free diet, and which, as noted by McCollum,<sup>15</sup> continues to the seventeenth day.

This experiment was performed with practically the same results on another dog except that during the first day of the injection period the food was vomited, owing to the animal having been fed too soon after etherization.

EXPERIMENT 2—A female dog weighing 6,230 gm was placed, on January 24, on a diet of 87 gm nitrogen-free butter, 98 gm cane sugar, 500 cc water and 1 gm sodium chlorid daily. The injection of dog-serum was made into a small vein of the leg under ether anesthesia. The results are shown in Table 2.

TABLE 2—SHOWING EXCRETION OF NITROGEN AND COAGULABLE PROTEIN IN EXPERIMENT 2

24 Hours Beginning 2 p m	Weight in Grams	Serum injected in c c	Nitro- gen of Serum in Gms	Volume of Urine in c c	Nitro- gen of Urine in Gms	Coagulable Protein
Jan 28	6,070			520	1.25	None
Jan 29	6,135			560	1.12	None
Jan 30	6,090			380	1.01	None
Jan 31	6,090	100	1.05	550	1.48	Vomited
Feb 1	6,020	80	84	425	1.14	Faint trace albumin
Feb 2	6,020	80	84	520	1.21	Faint trace albumin
Feb 3	5,880	80	84	340	1.07	Faint trace albumin
Feb 4	5,955			330	0.98	Faint trace albumin
Feb 5	5,890			410	0.99	Faint trace albumin

The urine was free from glucose and diacetic acid. On January 29 a control anesthetization was done quite similar to that used during the injections. Omitting the analysis on January 31, which is rendered worthless by the vomiting, we find the average elimination for five days, the three days before commencing, and the two days after ceasing injection, to be 1.08, the average elimination during the three days of injection 1.14. Here again we may conclude that practically all the nitrogen of the serum was utilized.

The same type of experiment was next tried with horse-serum instead of dog-serum. The horse-serum was obtained fresh and without preservative.

EXPERIMENT 3—A female dog, weighing 6,375 gm was placed, on January 22, on a diet of nitrogen-free butter and cane sugar the quantities being gradually increased until January 31 when the diet was fixed at 10 gm butter, 113 gm sugar, 300 cc water and 1 gm sodium chlorid daily. The horse serum was injected into a small vein of the leg under ether anesthesia. The results were as shown in Table 3.

TABLE 3—SHOWING EXCRETION OF NITROGEN OF URINE AND COAGULABLE PROTEIN IN EXPERIMENT 3

24 hours Beginning 2 p m	Weight in Grams	Serum injected in c c	Nitro- gen of Serum in Gms	Volume of Urine in c c	Nitro- gen of Urine in Gms	Coagulable Protein
Feb 1	5,880			350	1.10	None
Feb 2	5,878			470	1.28	None
Feb 3	5,815			275	1.06	None
Feb 4	5,850	80	74	430	1.23	None
Feb 5	5,750	80	74	450	1.35	None
Feb 6	5,810	80	74	290	1.23	None
Feb 7	5,780			180	1.10	Trace

Traces of glucose and diacetic acid were found on February 7, and as appetite failed at this point the experiment was brought to an end. In this experiment the average elimination of the three control days of the fore period and the one day of after period was 1.13, of the three days of injections, 1.27. Here also it is evident that the serum has been completely or almost completely utilized. A second similar experiment, owing to the larger amount of serum injected, gave even more conclusive results.

EXPERIMENT 4—A female dog, weighing 7.070 gm, was placed on a diet of nitrogen free butter and cane sugar, on March 2. From March 14 to 16 it received daily 8 gm of nitrogen free butter, 100 gm cane sugar, 500 cc water, and 1 gm sodium chlorid, from March 17 to 21 the butter was reduced to 6.5 gm daily. The horse serum was injected into a small vein of the leg, under ether anesthesia.

TABLE 4—URINE NITROGEN AND COAGULABLE PROTEIN EXCRETION IN EXPERIMENT 4

24 Hours Beginning 2 p. m.	Weight in Grams	Serum injected in c c	Nitro- gen of Serum in Gms	Volume of Urine in c c	Nitro- gen of Urine in Gms	Coagulable Protein
March 15	6,330			425	1.33	Very faint trace
March 16	6,360			155	1.36	Very faint trace
March 17	?			500	1.37	Very faint trace
March 18	6,275	120	1.60	480	1.52	Very faint trace
March 19	6,180	100	1.32	447	1.19	Very faint trace
March 20	6,120			305	1.11	Very faint trace
March 21	6,110			333	1.11	Very faint trace

No glucose or diacetic acid appeared in the urine. Here again is presented definite evidence of complete or almost complete utilization of the foreign serum. Whether the slight rise noted in both Experiments 3 and 4 is a coincidence or is due to a small fraction of the serum that is not utilized and is therefore eliminated, or is due to a toxic action of the serum, causing a slight increase in catabolism, it has been impossible to determine. Toxic action however, is rendered improbable by the fact that no increase in temperature was noted during the period of serum injection.

We believe that these experiments demonstrate, so far as can be shown by the chemical method, that the dog is able to utilize completely, homologous serum, parenterally introduced and completely, or almost completely, horse-serum similarly introduced. We differ therefore, from Friedenwald and Isaac, who concluded that the dog cannot utilize parenterally introduced horse-serum. We believe that their conclusions based on their chemical studies, are incorrect owing to the method they employed, that is the use of dogs either fasting or on a nitrogen balance. It is also worthy of note that the marked toxic effects which they noted in dogs receiving injections of horse-serum after being fed on a flesh diet

(usually horse flesh) were absent in our experiments with a butter and sugar diet. Also their observations on the persistence of horse-serum protein injected intravenously into the dogs, as measured by the complement deviation test, is of much interest in connection with our chemical studies. The gradual diminution, beginning soon after injection and continuing for several days, which they demonstrated in the amount of the complement deviating substance persisting in the circulation of the injected dog, is precisely the gradual diminution that one must expect if, as we believe, the horse-serum protein distributes itself evenly throughout the blood of the injected dog and is gradually utilized by the dog, simultaneously with the dog's own blood protein, at a rate proportional to the foreign protein's concentration in the dog's blood. We believe, therefore, that the complement deviation experiments of Friedenwald and Isaac with our own chemical studies afford strong evidence that the dog can utilize both homologous serum and horse-serum, introduced intravenously, as a source of tissue nitrogen.

#### CONCLUSIONS

1 In order to use changes in the elimination of nitrogen as a basis for deductions concerning the utilization of nitrogenous substances parenterally introduced, the animal must be on a calorically adequate, nitrogen-free diet.

2 A dog on such a diet and receiving intravenously an amount of nitrogen, in the form of dog-serum, approximately equal to that being eliminated, shows no increased elimination of nitrogen.

3 When a foreign serum, as horse-serum, is injected instead of dog-serum, the nitrogen elimination is increased very little, if at all.

4 The dog, therefore, is able to utilize completely for anabolic processes the protein of dog-serum and all, or almost all, of the protein of horse-serum introduced intravenously.

## "LOW FEVER"

T H WRIGHT, M D, AND W ALLAN, M D  
CHARLOTTE, N C

For a number of years, but during the past summer particularly, our attention has been directed to a clinical picture variously known as "continued fever," "sun fever," "Wilmington fever," "low fever," etc, the only constant symptom of which is a supposedly continuous elevation of temperature. That this supposition is incorrect can be easily determined by taking the temperature throughout the twenty-four hours, when it will be found that during the night the "fever" disappears. But as these patients do not feel ill, and do not go to bed, they are seen by the physician only during the day, hence the idea of a continuous elevation of temperature. As very little has appeared in the literature concerning this condition, a fuller description of this so-called "low fever" seems desirable, more especially for the sake of differential diagnosis.

The causes of continued fever in the northern part of the temperate zone, as laid down by Cabot<sup>1</sup> for New England, are typhoid fever, tuberculosis and sepsis. In the southern states there must be added as causes of continued fever the malarial fevers,<sup>2</sup> Malta fever,<sup>3</sup> hepatic abscess of amebic origin,<sup>4</sup> and in the tropics typanosomiasis and kala azar.

In this locality the chief difficulty lies in differentiating tuberculosis, for during the past decade a mass of accurate statistics on the prognosis of tuberculosis has become available showing that the earlier the diagnosis is made and the sooner treatment is commenced, the better are the chances for arrest or recovery. This showing has naturally increased the desire for the earliest possible diagnosis.

The various tuberculin reactions and the Roentgen ray have taught us that periods of malaise with a rise of a degree in temperature, are frequently the manifestations of a slight or of an early tuberculous infection, even in the absence of physical signs in the chest and of clinical pulmonary symptoms.

In this particular locality the tropical fevers, including æstivo-autumnal malarial fever,<sup>5</sup> are unknown, so that after excluding amebic

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1 Cabot, R C. The Three Long Continued Fevers of New England. Boston Med and Surg Jour, Aug 29, 1907, Differential Diagnosis, p 389

2 Craig, C F. The Malarial Fevers 1909 Wm Wood & Co

3 Feienbaugh, T L. Endemic Mediterranean Fever (Malta Fever) in Southwest Texas Jour Am Med Assn, 1911, xlvii, 730

4 Rogers, L. Fevers in the Tropics, ed 2, p 379

5 Allan, W. Charlotte Med Jour, 1911, lxi, 165

hepatitis and amebic abscess of the liver, malaise with a slight daily rise of temperature without leukocytosis should be considered presumptive evidence of a tuberculous infection. But we submit that an early diagnosis cannot be made by exclusion in this latitude, and that the cases so diagnosed are subjected to unnecessary mental anguish and their condition is thereby aggravated, because of such a diagnosis.

In the tropics this "low fever" was some years ago singled out from among the unclassified non-specific continued fevers.

#### HISTORICAL

In 1894 A Crombie<sup>6</sup> (a) gave a very good description of this condition as follows

It is one which is only occasionally met with among Europeans, and I do not think I have met with it in the natives in India, but if it does occur among them it would hardly be brought under my notice. I refer to a persistent low elevation of temperature unaccompanied by any constant symptoms of definite duration, and uninfluenced either by quinin or arsenic. The temperature never falls below 99 degrees and rarely rises above 101.5. It may continue for several weeks without complication except, perhaps, a tendency to diarrhea of a bilious character, with loss of appetite, and gradual loss of strength and flesh. Some of these cases are distinctly aggravated by quinin, and I have known them cease abruptly on withdrawing the drug which had been persistently given in the belief that the condition was malarial in its essential nature. These cases are spoken of as "low fever" and are generally cured by a "change" of any kind, but especially by a trip to sea, and it is especially this form of fever, which in Calcutta is benefited by a visit to the sandheads. Though very ill-defined, these cases constitute a distinct type of fever at once recognized when met with.

At the same time Ronald Ross,<sup>7</sup> giving a classification of fevers for India, under the heading of simple or continued fevers, gives a subhead to "fever without any concurrent symptoms."

Again, in 1898, in his classification of "non-specific fevers of doubtful causation, probably climatic," Crombie<sup>6</sup> (b) gives four classes, the last of which is "low fever."

In speaking of the effect of exercise on temperature he says

And the gradation of symptoms from the mere temporary elevation of temperature which invariably accompanies exercise in the hot moist climate of Bengal (I have known my own temperature rise to 99.9 F as the result of an hour's walk in the month of August) though a few hour's febricula or a few days of continued fever, up to ardent fever and siriasis, point rather to their being the result of a temporary paresis of the heat regulators under the embarrassments of the conditions of high temperature and humidity.

<sup>6</sup> Crombie, A. (a) Presidential Address on the Fevers of India. *Tr First Indian Med Cong*, 1894, p 17, (b) *The Unclassified Fevers of Hot Climates Brit Med Jour*, 1898, 11, 682, *Jour Trop Med*, p 128.

<sup>7</sup> Ross, R. *Tr First Indian Med Cong*, 1894 p 382.



In describing this low fever he says

Low fever is of a distinctly different type from the foregoing climatic fevers (Nasha fever, etc.) It is characterized by a persistent low elevation of temperature of indefinite duration, without any specific symptoms, except those traceable to the feverish condition itself. It begins insidiously with slight malaise and anorexia. The temperature ranges from 99 F in the morning to 101.5 F in the evening, never falling below 99 F and rarely rising above 101 F, and it may continue for many weeks unaffected by quinin or arsenic, pushed to extreme doses, or by any other medicinal treatment, but usually yielding at once to change of climate. It would appear also to be due to embarrassment of the heat centers, because it ceases generally at once when the climatic conditions are improved by the patient going to the hills or to the sea. If it were due to a specific cause this would not be the case. If it were due to a microorganism in the blood, the cessation of the symptoms would not be as immediate as happens so constantly with this form of fever on change of climatic surroundings.

Manson<sup>8</sup> gives practically the same account of "low fever" as Ciombie and speaks of it as "not an unusual one among Europeans in the tropics."

Rogers<sup>9</sup> description of "low fever" is probably the best in the literature. He has encountered it in Europeans in the hot damp provinces of Bengal, Assam and Madras. His clinical description includes malaise, anorexia and nervous depression, with a rise of temperature during the daily activities to 99 F or 100 F, or rarely to 101 F, with a return to normal during the early morning. The fever may continue through the next cold season, though, with Ciombie, he finds that a change to a higher, drier or colder climate causes immediate abatement of the temperature. Physical examination is negative, although he makes the surprising statement that "in very long cases some enlargement of the spleen may ultimately develop." He finds generally a leukopenia with a relative increase in the small mononuclear leukocytes to about 40 per cent and a decrease of the polymorphonuclears to about 50 per cent, but with no marked increase in the large mononuclears. Rogers also suggests "an enfeeblement of the heat-regulating mechanism by prolonged strain as the essential cause of the excessive diurnal variation of the body temperature which occurs." He suggests the possibility of a leukocytozoan parasite, and cites the experience of Musgrave, Wherry and Woolley<sup>10</sup> in Manila. His reference to Castellani's<sup>11</sup> four cases was probably not intended to refer to this class of fever, as all of these cases were clearly infectious, and only one bore any near resemblance to "low fever" clinically, in this case there was severe diarrhea, and a bacillus was isolated from the feces which was agglutinated by the patient's blood.

8 Manson, Sir P. Tropical Diseases, ed 4, p 320

9 Rogers, L. Fevers in the Tropics, ed 2, 1908, p 193

10 Musgrave, W. E., Wherry, W. B., and Woolley, P. G. Tropical Splenomegaly. Bull. Johns Hopkins Hosp., 1906, xviii, 28

11 Castellani, A. Notes on Cases of Fever Frequently Confounded with Typhoid and Malaria in the Tropics. Jour. Hyg., 1907, vii, 1

The description of "low fever" by Chalmers and Castellani<sup>12</sup> seems to apply to this infectious fever of low virulence, rather than to the clinical picture as first described by Crombie

In our own cases we have encountered this low fever in persons who were overworked and underfed. Our series comprises three men and six women. It seems to be confined to the most active period of life, between the ages of 15 and 40 years. Our observations on negroes are too incomplete to compare its race incidence. Social condition and occupation seem to be without effect. Overstrain, mental or physical, is the predisposing cause. These cases all show loss of weight, a secondary anemia of varying degree and poor muscular tone. Their time is spent mostly indoors, and practically no exercise is taken. The caloric value of their diet is always considerably below normal, running from 20 to 28 calories per kilo of body-weight. The usual fatigue symptoms are in evidence, anorexia, nausea, flatulence, constipation or the early morning diarrhea which is liable to accompany any condition in which there is low blood-pressure (as pellagra, sprue, etc.), headache, vertigo, insomnia, early mental and muscular fatigue, backache and aching in the legs and knees.

The physical examination has been uniformly negative. There is no cough, sputum or night sweats, and all cases showing a positive von Pirquet tuberculin reaction have been excluded. The throats were gone over carefully, and all cases in which pus could be squeezed from the tonsils have been excluded from this series. We have found blood-pressure ranging from 90 to 115 mm Hg. In some cases the pulse-rate has been increased. Hemoglobin estimations ran from 65 to 90 (Talqvist). In only a few instances were we able to confirm Rogers' findings of leukopenia with relative increase in the small mononuclear leukocytes and decrease in the polymorphonuclears. *Plasmodium vivax* (the only form of malarial organism occurring in Charlotte) was never present.

The fever curve itself was the only thing characteristic of the condition. Contrary to Crombie's statement, we find with Rogers, that the temperature returns to normal during the night, but contrary to Rogers' statement that the elevation of temperature makes its appearance in the middle of the day or early afternoon, we find it frequently appears during the first hour after rising in the morning, or following the first meal of the day, and, furthermore, that the temperature may fall below 99 F and rise again at any time during the day. Usually the daily temperature has varied between 99 F and 100 F, but at times reaching 100.6 F. This "low fever" generally appears about June, after a month's hot weather, and continues until the cooler weather of October, or until a vacation is taken. In cases that have recently become "run down" it may appear

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<sup>12</sup> Castellani and Chalmers. Manual of Tropical Diseases, p. 789

TABLE GIVING ANALYSIS OF

Case	1	2	3	4
Color	M S White	A C White	E E White	W A R White
Sex	Male	Female	Female	Male
Age	30	24	21	38
Social Condi- tion	S	S	S	M
Occupation	Druggist	Stenographer	Teacher	Businessman
Predisposing Causes	Steady over- strain	Nursing	Steady over strain	Influenza 1 mo ago
Duration of Fever	4 mo in 1910	2 mo in 1910	5 mo in 1911	2 mo in 1911
Recurrences	None	1908 1909 1910 1911 1912		
Hours of Sleep	8 5	8	8	8
Hours of Work	13	9	7	8
Amount of Exercise	Standing all day	1 mile walk	None	1 mile walk
Diet	26 calories per kilo	24 calories per kilo		.
Weight	11 lbs off in 4 mo	18 lbs off for 4 yrs	6 lbs off	Normal
Headache	None	Every 10 days	None	None
Insomnia	None	None	None	None
Tongue	Coated	Coated	Normal	Coated
Stomach	Sour	Sour	Attacks of pain when nervous	Nausea at times
Appetite	Poor	Poor		
Intestines	Constipation, Gas	Constipation, Gas	.	Takes daily purge
Pulse rate	80	80	85	124
Blood-pressure		100		
Muscular Tone	Worn out, aching by night	Very poor	Can hardly drag home	Fair, tired
Backache	Present	Present	Absent	Absent
Cough,	None	None	None	None
Sputum,	None	None	None	None
Night-sweats	None	None	None	None
Tuberculin Reactions	Negative to von Pirquet	Negative to von Pirquet	Negative to von Pirquet Calmette, Koch	Negative to von Pirquet
White count		6,700	6,000	8,200
Differential				
Polynuclear		64%	80%	71%
Small monos		24	15	18
Large monos		8	5	8
Eosinophils	5 4%	4	0	3
Hemoglobin	78%	80%	90%	80%
Red Count	4,320,000	4,470,000	5,000,000	4,000,000
Color Index	89	89	90	1 00
Plasmodia	Negative	Negative	Negative	Negative
Feces	Normal	Normal	Normal	
Urine	Conc	Normal	Normal	Normal
Complications	None	Visceroptosis	None	None

AUTHOR'S CASES OF "LOW FEVER"

5	6	7	8	9
E B D White Female 38 W	E White Female 21 S	J C T White Female 30 M	J E S White Male 40 M	G White Female 34 W
Stenographer Steady over strain 3 mo in 1911  1912	School-girl Typhoid 3 months ago 1 mo in 1911	Housewife 5 pregnancies in 7 years 1 mo in 1911	Manufacturer Worry  4 mo in 1911	Nurse Worry  6 mo in 1911
9 9 1 mile walk  28 calories per kilo 7 lbs off  Frontal (often)  Severe  Normal Anorexia	8 7 None  18 lbs off in 9 mo Frontal a week at a time At times  Normal Normal	8 15 Standing all day .. 24 lbs off  Frontal  None  Normal Acid, Gnawing	8 5 6 None  20 calories per kilo 20 lbs off  None (has vertigo)  None  Coated Anorexia	8 5 9 Standing all day 21 calories per kilo 31 lbs off  Frequent for 3 years  Came on as wt decreased Normal Frequent Nausea
Bilious, con- stipated, gas  82 to 106 Low Feels weak	Normal  90  General weakness	Takes daily purge  60 to 70  Tired in half a day	Diarrhea (early morn- ing) gas 80 to 100 90 Poor	Constipated 4 years  95 Poor
Present None None None Negative to von Pirquet	Present None None None Negative to von Pirquet	Present Negative None None	Absent None None None Negative to von Pirquet	Present None None None Negative to von Pirquet
	9,200  64% 25 6 5 85%	8,000  70% 24 6 0 65% 3,880,000 83	7,000     90% 4,500,000 1 00	5,000 Normal    85% 4,500,000 94
Negative  Retroflexion	Negative Normal Alkaline None	Negative Normal Indican None	Negative Normal Normal None	Negative Normal Very Acid None

later in the summer, and in chronic cases it may continue interruptedly throughout the winter. In some of our cases it has recurred with great regularity every summer for a number of years.

A vacation to the coast or mountains may put an end to the "fever" at once, but this is particularly true of a change to the higher mountain resorts of the state, such as Blowing Rock (elevation 4,000 feet), where the nights are cold. For the sake of brevity we have tabulated our cases.

We believe that this "low fever" is simply an abnormal diurnal variation of the body temperature, due to a temporary instability of the heat-regulating mechanism as stated by Crombie and by Rogers, this depression of the heat-regulating function being merely one expression of a general functional depression or state of chronic fatigue, dependent on under-nutrition and over-strain, and emphasized especially during the summer of 1911 by the unusual heat.

We shall proceed to discuss this proposition.

Butler<sup>13</sup> gives the range of normal temperature as from 97.2 F. to 99.5 F., the average being 98.6 F. Both Butler and Howell<sup>14</sup> state that muscular exercise may raise the temperature. Howell stating that if this initial rise of temperature occurs it is a sign of imperfect heat regulation, that is, the extra amount of heat thus produced is not promptly gotten rid of. Both state that meals may raise the temperature, Butler giving as much as 0.4 F. Wunderlich's figures as given by Adams<sup>15</sup> are sub-febrile to 100 F., low febrile to 100 F. to 101 F., moderately febrile 101 F. to 103 F., etc.

Heat production depends on the intake of food and on muscular exercise, heat loss depends on excretions (2 per cent), on expired air (3.5 per cent) and evaporation of water from the lungs (7 per cent), on the evaporation of sweat (14 per cent), and on radiation and conduction from the body surface (73 per cent). Heat regulation is controlled mainly by sweating and radiation. "The control through the vasomotor nerves is doubtless even more important" (Howell), that is, dilatation of the skin capillaries means loss of heat, cold air contracts the skin capillaries and conserves heat. Howell says that neither heat centers nor heat nerves have been demonstrated, and further that,

Most physiologists perhaps believe that variations in heat production occur, as stated above, by alterations in the intensity of oxidations in the muscles, brought about by reflex excitation through the motor nerve fibers and that a special set of heat fibers does not exist. The unconscious regulation of the body temperature is effected chiefly through the following centers:

Heat Dissipation 1. Sweat centers and sweat nerves 2. Vasoconstrictor center and vasoconstrictor nerves 3. Respiratory center

Heat Production 1. Motor nerve centers and motor nerve fibers to skeletal muscles 2. Quantity and character of food as determined by the appetite

13 Butler. *The Diagnostics of Internal Medicine*, ed. 2, 1906, p. 107.

14 Howell. *Text Book of Physiology*, 1906, p. 828.

15 Adams. *Principles of Pathology*, ed. 2, 1, p. 481.

On the other hand, Adam<sup>15</sup> says

We must with MacAlister, predicate the existence of some central heat-controlling center regulating the (various) heat-producing and heat-discharging apparatus, a center which stimulates the former and inhibits the latter in order to raise the body temperature, and does the reverse in order to lower it. All that is sure is that within the brain and spinal cord are nerve cells, which on stimulation lead, some of them, to increased production of heat by the tissues, others to increased loss of heat by the body surfaces. The wonderful regulation of the bodily temperature under ordinary conditions is a strong indication that controlling the production and the loss is one pair or an intimately connected system of heat-regulating centers.

As applied to our cases it seems obvious that their increase in temperature cannot be due to extra heat production by muscular activity, or increased food intake, as both of these functions are diminished, there must be, then, imperfect heat elimination. This diminished heat dissipation is not due to slower respiration, nor to vasoconstriction (there is vasodilation), it must be due then to either diminished radiation and conduction, or to imperfect evaporation from the skin, or to both. That diminished radiation and conduction play a considerable part in this condition is shown by the fact that these temperatures were recorded during the hot weather, and in the daylight, and that they returned to normal with the advent of cold weather. But diminished radiation and conduction alone is not a sufficient explanation, for, although the temperature rises when the daily activities commence, there is a definite limit in each case beyond which this rise will not go. What then fixes this limit and keeps the temperature below it? It must be the effect of the body heat on the sweat nerves, causing reflexly an increased sweating, with consequent loss of heat. H. Aron<sup>16</sup> has demonstrated that animals exposed to the tropical sun soon die unless increased evaporation of water counteracts the increased heat absorption. He says, "Monkeys exposed to the sun in Manila die in a little over one hour because of their limited capacity to evaporate water, while man with his well-developed sweat glands resists the same climatic conditions for a much longer period without detriment", and again, "The more perfect this water evaporation is, the better the normal body temperature may be maintained." In noting the inferiority of the white man to the black in effective sweating, he says, "It is as yet undecided whether the result is due to the color, or if the nervous regulation of the sweat glands, etc." He evidently considers the evaporation of sweat to be the method of heat regulation, as after exercise, even in temperate climates.

In comparing the action of the tropical sun on the skin temperature of Filipinos and Americans, he says

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<sup>16</sup> Aron, H. *Philippine Jour. Sc.*, Section B, 1911 vi, 126

With the white skin this process (evaporation) takes place more slowly and it must be for this reason that the brown skin, while absorbing more heat, is found to have lower temperatures than the white skin under similar conditions. The regulatory apparatus of the brown is more sensitive and works more promptly and successfully.

Chart 1—Effect of the unusual heat of the summer of 1911 in producing "low fever."

In these fatigue cases with general lowering of the functions, during normal activity in the season when radiation and conduction are lessened, the body temperature is regulated at from 99 to 100  $\pm$  during the day time. This phenomenon seems to be due to the lack of sensitiveness of the sweating arc to a moderate increase in the body temperature in these individuals and during ordinary activity the threshold of stimulation of the sweating arc seems to be raised from 0.5 F to 2 F.

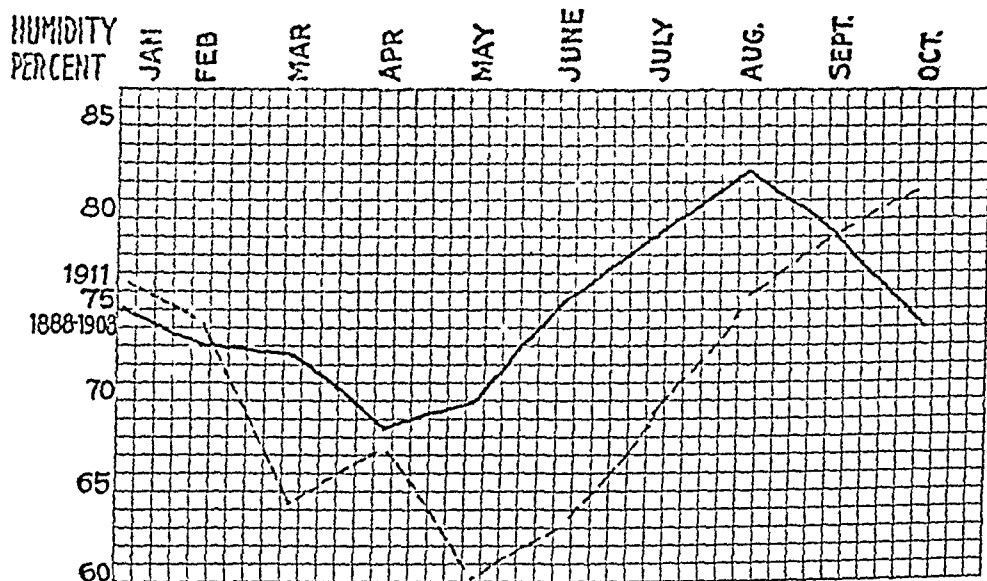


Chart 2—A chart showing the average of morning and evening humidity in 1911 compared with the twenty years, 1888-1908, by months. (These data were obtained from the weather bureau office, Charlotte, through the kindness of Mr Atto, Chief Observer.)

That this depression of the heat-regulating function is merely one expression of a general functional depression is easily apparent from the case series. That undernutrition and overstrain were present is also apparent from the accompanying chart, and in the absence of any other

demonstrable etiologic factors, these must be considered as the two chief causes of this condition. The part played by the unusual heat of the summer of 1911 can best be shown by Chart 1.

From May 1 to Nov 1, 1911, 184 days, there were 131 days above the average temperature, thirteen days of average temperature, and forty days below the average temperature; from May 10 to October 23, 166 days, there were 128 above, ten equal to, and twenty-eight below the average temperature.

The severity of this heat was considerably modified by the low humidity, as shown in Chart 2.

The marked benefits to be derived from a change of scene are due to a relief from overstrain, and in many instances this is the only treatment needed to stop the "fever." In the more stubborn cases an improvement in nutrition is necessary before the temperature falls to its usual level, as is shown during the winter, when these patients regain their appetites and put on a little flesh.

The advantage of removal to high mountain sections over the Piedmont or tide-water regions, we believe, is entirely due to the cold, which restores appetite and promptly raises blood-pressure.

In conclusion then, we would point out that in the south we have a low fever, occurring during the summer months, which is only apparently continuous, and which is purely functional.



# AN EXPERIMENTAL INVESTIGATION OF THE VALUE OF HEXAMETHYLENAMIN AND ALLIED COMPOUNDS<sup>\*</sup>

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This study was undertaken to determine the capacity of infected kidneys to excrete hexamethylenamin. We had just had a small series of unilateral kidney infections in which large doses of hexamethylenamin had failed to be of any benefit. The frequent clinical failure of the drug it was felt might depend on its inability to pass through such impaired organs. At the outset, full credence was placed in the generally current valuation set on hexamethylenamin, i. e., when taken by mouth, it is excreted in the urine, bile, pancreatic, synovial and cerebrospinal fluids in sufficient quantities to be of marked bactericidal value. This confidence, however, was not strengthened by a rather thorough review of its extensive literature, and personal experimental results which quickly developed gave still greater uncertainty. Ever since Nicolaier introduced it into medicine nearly twenty years ago, the efficiency of the drug has been ascribed to its decomposition into formaldehyd. The authors, however, are quite vague, using such adjectives as, a little, partial and almost complete, in describing the extent of this decomposition, and not a few hold that hexamethylenamin is antiseptic itself independent of the formation of formaldehyd.

Nowhere has there been serious endeavor to ascertain how much hexamethylenamin or formaldehyd are present in the fluids of the body after giving the drug by mouth. Its accredited efficiency in the body fluids where it has been described, rests first, on a demonstration of the existence of either hexamethylenamin or formaldehyd in the fluid, second, on clinical improvement, and third, on the reduction in the number of bacteria as shown by the plate-culture methods after its use. In my personal studies, the seemingly necessary steps were, first, a quantitative determination of the amount of hexamethylenamin excreted in the urine after giving known quantities by mouth, second, a quantitative estimation of the amount of free formaldehyd present, third, determination of the bactericidal power of hexamethylenamin, fourth, determination of the bactericidal power of formaldehyd, fifth, determination of the strongest solutions of hexamethylenamin and of formaldehyd which can be tolerated by the kidneys and other urinary organs, sixth, a comparison of the chemical and clinical findings.

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<sup>\*</sup>Manuscript submitted for publication in ARCHIVES July 11, 1912

The third, fourth and fifth steps proved simple and yielded positive results, the details of which follow. Great difficulty, however, was met at the very outset in connection with securing suitable chemical methods for estimating the amounts of the substances in the fluids. Not only were the quantitative methods uncertain, but the qualitative procedures were equally unsatisfactory, principally because they reacted identically with hexamethylenamin and formaldehyd.

The most delicate qualitative test in use and one which has been extensively employed is that of Hehner. It consists in adding 5 or 6 drops of milk to a few c c of the fluid to be tested. This mixture is then stratified over a reagent made by adding one drop of a 3 per cent ferric chlorid solution to 100 c c of 99 per cent sulphuric acid. The presence of formaldehyd or hexamethylenamin is indicated by the slow formation at the line of juncture of a deep amethyst ring. The color of urine and bile seriously interfere with the test and require a preliminary distillation, which is accomplished by adding a little sulphuric acid and water, when formaldehyd gas passes off in the distillate.

The objections to this test are two-fold. First, that it does not differentiate between formaldehyd and hexamethylenamin, and second, because of its extraordinary delicacy. Formaldehyd clearly shows in solutions of 1 to 1,000,000 and hexamethylenamin in solutions of 1 to 500,000 or less. This is in the proportion of 1 c c of formaldehyd to 1,000 liters of water. By the thickness of the ring or the rapidity of its appearance I was completely unable to distinguish between solutions of 1 to 100,000 and 1 to 10,000, nor could I determine from the ring formation whether formaldehyd or hexamethylenamin was the substance present.

Through the valuable assistance of Dr. H. A. B. Dunning, I was fortunate in securing a very delicate test and one which reacts to free formaldehyd, but not to hexamethylenamin. This test consists in adding to the suspected fluid, 3 drops of 5 per cent aqueous solution of phenylhydrazin hydrochlorid and then 3 drops of a 5 per cent aqueous solution of sodium nitroprussid, then an excess of saturated aqueous solution of sodium hydroxid. It is important that the solution to be tested as well as the sodium hydroxid be slightly warmed to a little more than body temperature. When formaldehyd is present in solutions of 1 to 20,000, or stronger, there follows an intense blue color which gradually changes to green and then after a few minutes to brown. In solutions of less than 1 to 20,000 the first color is the intense green which passes off into brown. The test is delicate down to 1 to 150,000 or less. When a solution is tested and found to be negative as is the case when hexamethylenamin alone is present, it can be acidulated with sulphuric acid, heated to boiling, cooled off and tested, when the reaction will be positive due to the breakdown of hexamethylenamin into formaldehyd. This has yielded striking results in the urine, the bile, the sputum, the saliva and the cere-

brospinal fluid, and so contradictory to the generally accepted beliefs that it seemed important to bring them to the attention of the profession. I have thus been diverted from my original purpose, the quantitative estimation of the hexamethylenamin and formaldehyd in the urine. I have at present a promising quantitative method for these determinations and will embody my findings with it in a later communication.

I wish to present here the results of my experiments in regard to the bactericidal powers of hexamethylenamin and formaldehyd, the toleration of the urinary organs to these substances, the question of the excretion of hexamethylenamin in the urine, the bile, the sputum, the saliva and the cerebrospinal fluids. In addition to hexamethylenamin, I have employed helmitol and several other formaldehyd compounds.

Before taking up the actual findings it seems desirable to give a short historical review of the subject.

Hexamethylenamin is formed by the direct action of four molecules of ammonia on six of formaldehyd gas. According to the formula  $4\text{NH}_3 + 6\text{HCO} = (\text{CH}_2)_6\text{N}_4 + 6\text{H}_2\text{O}$ . It occurs as colorless, odorless crystals, which are readily soluble in water, less so in alcohol. It was first prepared by Butlerow.<sup>1</sup> When acid is added to an aqueous solution there is partial decomposition into formaldehyd and ammonia and on boiling, complete decomposition. Boiling alone partly causes decomposition. The drug was introduced into medicine as a urinary antiseptic by Nicolaier,<sup>2</sup> and has ever since enjoyed wide popularity and extensive use all over the world. It remained as a urinary antiseptic alone until S. J. Crowe<sup>3</sup> gave it reputation as a gall-bladder and pancreatic disinfectant, and one year later<sup>4</sup> brought it into its present use as a prophylactic and curative agent in cerebrospinal infections. Armstrong and Goodman<sup>5</sup> following Crowe's method, introduced it into use as the disinfectant of the sputum in bronchitis, pneumonia, pulmonary tuberculosis and infections of the nose and throat. After giving it by the mouth, it has been found in the aqueous humor of the eye, in the synovial and pleural fluids. Many clinical contributions of a more or less confirmatory nature have been added and the use of the substance "as a bactericide" in these conditions has grown almost to equal its use as a urinary antiseptic.

#### TOXICITY OF HEXAMETHYLENAMIN

In the rabbit hexamethylenamin is practically non-toxic. I have given 100 grains at a dose, hyperdermically, without the slightest evidence of poisoning. This animal weighed 2 pounds, so that the equivalent dose in

1 Butlerow. Liebigs Ann. d. Chem. u. Pharm., 1860, cxv, 322.

2 Nicolaier. Deutsch. med. Wchnschr., 1895, No. 34.

3 Crowe, S. J. Bull. Johns Hopkins Hosp., 1908, xiv, 109.

4 Crowe, S. J. Bull. Johns Hopkins Hosp., 1909, xv, 102.

5 Armstrong and Goodman. Jour. Am. Med. Assn., May 27, 1911.

the human being of 150 pounds, would be about 18 ounces. However, there is one marked difference between the human being and the rabbit, i e, in the rabbit, even on immense doses, there is no decomposition into formaldehyd. The drug is excreted as hexamethylenamin. The toxic effects noted in the human being have been hematuria and vesical irritation, both due to a liberation of formaldehyd gas in the urine at the level of the kidney.

#### BACTERICIDAL POWERS OF HEXAMETHYLENAMIN AND FORMALDEHYD

The technic employed was uniform, i e, solutions of varying strength of each drug in sterile water were made. These solutions were then inoculated with the bacteria tested so that a slight clouding of the fluid was produced. The inoculated tubes were then incubated at body temperature in periods varying from a few minutes to a week. The bacteria employed were the colon bacillus, the typhoid bacillus, the bacillus pyocyaneus, the streptococcus and the staphylococcus aureus.

Hexamethylenamin solutions free of formaldehyd were obtained by adding a drop of ammonia to each tube. The hexamethylenamin proved to have no bactericidal power, the organisms tested all lived in from 5 per cent to 10 per cent solutions without any deterioration.

The formaldehyd solutions, on the contrary, proved very bactericidal. A solution of 1 to 100 destroyed all the organisms studied in twenty minutes. A 1 to 1,000 solution destroyed all of them within twenty-four hours. Marked differences in the toleration toward formaldehyd was noted between the different bacteria. The most resistant organism was the *Staphylococcus aureus*, and the least resistant, the typhoid bacillus. A solution of 1 to 5,000 formaldehyd destroyed the typhoid bacillus and the streptococcus within twenty-four hours. It destroyed the *Bacillus pyocyaneus* within forty-eight hours, and the colon bacillus in four days. The *Staphylococcus aureus* was still alive at the end of a week. The *Staphylococcus aureus* was completely destroyed in forty-eight hours by a solution of 1 to 2,000 formaldehyd. Solutions of 1 to 20,000 formaldehyd had little or no effect on any of the organisms except the typhoid bacillus and the streptococcus, these were not destroyed at the end of four days, but as shown by reinoculations, were somewhat diminished in vitality. A 1 to 50,000 formaldehyd solution had apparently no effect either in destroying the organism or in inhibiting their growth.<sup>6</sup>

#### TOXIC EFFECTS OF FORMALDEHYD

In dilutions of 1 per cent and less, formaldehyd solution is an irritant to the skin, in weaker solutions it is not irritant. Every year there are a few reports of serious poisonings resulting from accidental or

<sup>6</sup> All were formaldehyd solutions made from a carefully standardized 10 per cent aqueous solution of the gas.

suicidal drinking of formaldehyd solutions. In a majority of the cases there are violent gastro-intestinal symptoms, and in the more serious ones, coma which may last several days. In the fatal cases, death has resulted from gradual paralysis of the cardio-respiratory system. So far as is known to me, there has never been a case in the human being of poisoning from hexamethylenamin due to liberation of formaldehyd in the tissues. Jacobson<sup>7</sup> states that dogs can take daily 3.2 gm without serious results. On the other hand, 1 c.c. per kilo is said to be lethal in a single dose. In association with Dr. H. A. Kelly, I have been using, locally, solutions of formaldehyd varying in strength from 1-250 to 1-7,500, in treating infections in various parts of the body and have never noted any general toxic symptoms.

#### TOLERANCE OF THE URINARY ORGANS TO FORMALDEHYD

Our method of investigation here was, first, to try various strengths of formaldehyd solution in the bladder, beginning with a very small percentage and gradually increasing it. Having found a solution which was well tolerated in the bladder, it was then injected into the kidney pelvis through a renal catheter. There are marked individual variations in the tolerance of the vesical mucous membrane to formaldehyd solution, and this is independent of the state of inflammation present. Of course, an acutely inflamed bladder is much more intolerant than a healthy bladder. In chronic cystitis and in healthy bladders we have found it practical to use solutions varying in strength from 1 to 3,750, to 1 to 7,500. Occasionally a bladder is met with which does not tolerate even this weak solution. We have had no cases which would not tolerate a 1 to 12,500 solution of formaldehyd. The kidney pelvis will tolerate solutions as strong as does the bladder, and we have never noted any irritation in the kidney itself after an irrigation.

The formaldehyd irrigations for bladder and kidney infections have proved very effectual. They are especially valuable in cystitis, associated with ammoniacal decomposition of the urine, such as occurs with enlarged prostate or tumor of the bladder.

The gall-bladder tolerates formaldehyd readily in solutions of 1 to 3,750. In infected incisions and sinuses, a 2½ per cent solution can be used without giving undue pain.

A few tests were made with solutions of hexamethylenamin. It is not at all irritating and can be used in the bladder and kidney in 50 per cent strength without any ill result, but apparently with no effect on the infection.

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<sup>7</sup> Jacobson. Berl. klin. Wehnschr., 1904, p. 114.

## EXCRETION OF HEXAMETHYLENAMIN IN THE URINE

When given by mouth, hexamethylenamin begins to appear in the urine in fifteen minutes, reaches its maximum excretion in two hours, continues to be excreted abundantly for about eight hours, and has, if the dose given was not greater than 30 grains, disappeared in twenty-four hours. After the twelfth hour, the amounts excreted are very small. In a communication to follow this, I will report more in detail the quantitative eliminative amounts of hexamethylenamin.

The question of interest here is, how much formaldehyd is present in the urine after giving hexamethylenamin by mouth? As yet, I have not sufficiently worked out this question, but can say roughly that in some patients it is possible to secure solutions of from 1 to 5,000, and stronger. My important finding was here that on the customary doses, of from 5 to 10 grains, given three times a day, not more than two patients out of ten showed any decomposition of the drug into formaldehyd at all. This was tested out, not only on patients suffering with infections of the urinary tract, but on a series of normal individuals, and on a number of patients convalescent from operations. When a patient was found to show abundant formaldehyd after a 10-grain dose, it also was found that a 2- or 3-grain dose often sufficed to show the breakdown. While not more than 10 per cent of those examined showed the formaldehyd free after the smaller doses, at least 60 per cent showed it when the dosage was made from 20 to 30 grains, repeated every four to six hours. In a few instances in which the formaldehyd was not present after dosage of 30 grains, the quantity was raised to as high as 100 grains at a single dose without causing a decomposition of the hexamethylenamin. There are some individuals who do not break down hexamethylenamin into formaldehyd. This, however, is the exception, not the rule.

## PLACE OF DECOMPOSITION

At what point in the urinary tract is hexamethylenamin transformed into formaldehyd? In every case in which free formaldehyd was found in the bladder urine and catheterization of the kidney carried out the formaldehyd was found at the level of the kidney. This fact was established in five successive patients. In one patient of this group the blood-serum was examined and found to contain hexamethylenamin, but no formaldehyd. It is my impression that the formaldehyd liberation is due to some specific activity of the renal epithelium. It is, of course impossible to conceive of free formaldehyd in a highly ammoniacal urine. The urine's alkalinity, however, is normally not due to free ammonia. The greatest decompositions have been observed in highly acid urines. This, however, is not invariably the case, and it was frequently noted that in an acid urine there was no free formaldehyd after giving the hexamethylen-

amin. The same thing holds for alkaline urine. With the reaction definitely alkaline, large amounts of formaldehyd are occasionally met with.

#### CLINICAL OBSERVATIONS

The clinical results obtained have conformed in every way with the assumption that it is the free formaldehyd which is the effective agent, and that it must be present in fairly strong solution. In not a single case has there been observed the slightest improvement from giving hexamethylenamin when the urine showed hexamethylenamin, but no free formaldehyd. On the contrary, every patient showing free formaldehyd has shown prompt improvement and a number of the very chronic and obstinate colon infections have entirely cleared up. To obtain this result the treatment in some cases had to be carried over several months.

A pertinent example of this kind was afforded by the case of Mrs. E. C. S., aged 29, first seen Oct. 26, 1911. This patient had always been healthy, and had had three normal labors. In March, 1911, when four months pregnant, she was seized with an attack of renal colic in the left kidney region and two days later had a similar one in the right side. She was allowed to continue the pregnancy and gave birth to a healthy child in July, 1911. From the very first attack, the patient began having pus and blood in the urine. This continued after the labor and was associated with irregular fever, marked deterioration of general health and great reduction in hemoglobin. In November, 1911, she had the kidneys catheterized, functional tests made, and (x-ray pictures taken) collargol injection of the pelvis. The results of these examinations were to show that there was bilateral colon bacillus infection of the kidneys, greatly dilated pelvis, the left having a capacity of 120 cc and the right of 320. The functions of the kidneys, however, were fairly well maintained, as shown by the phenolsulphonephthalein test. Ten grains of hexamethylenamin by mouth sufficed to give free formaldehyd from both kidneys. At the time of the examination there was an enormous amount of pus on both sides. The patient was started on 120 grains of hexamethylenamin per diem. This occasionally caused vesical distress, when the dose was reduced. By February 3, the urine had practically cleared of infection. On that date Dr. Kelly suspended and plicated the pelvis of the right kidney. On the twentieth of the same month a similar operation was carried out on the left side. The hexamethylenamin was continued during her stay in the hospital. A recent examination shows a perfectly sterile urine, free from pus and blood.

#### THE DOSAGE OF HEXAMETHYLENAMIN

The average dose advised for hexamethylenamin is 7.5 grains, repeated two or three times per diem. In an occasional case of irritable bladder, even this amount causes a sufficient liberation of formaldehyd to produce irritation. Such, however, is the exception. If it does cause irritation, free formaldehyd will always be found and the indication is to reduce the dose. From what has been said, it is evident that there is no fixed dose. This is to be obtained by testing the urine and observing the toleration of the patient. Where 10 grains causes no free formaldehyd liberation, the dose should be increased to 20 grains and if there is still none, to 30 or 40 grains, repeated every four hours. The only toxic effect due to

hexamethylenamin is occasioned by the liberation of formaldehyd in the urine, and when this does not occur, it is safe to push the dose until it does appear. The first disagreeable symptom in our experience is vesical irritability. It has always led us to discontinue or diminish the dose. In such a case, pushing the dose might easily lead to hematuria. We have never observed a macroscopic hematuria from the use of hexamethylenamin.

The proper treatment is to give a dose just large enough to be under that necessary to cause bladder irritation. Using this dose, improvement will follow so rapidly in most cases that long continuation in the use of the drug is unnecessary. On the other hand, it is certainly possible to keep up the dosage for months without any serious impairment of either the general health or of the kidneys.

#### SOME OF THE PROPRIETARY HEXAMETHYLENAMIN COMPOUNDS

The first trade name and one which has been so universally used as to have become fixed in the popular mind is urotropin. It is, however, sold under various other names, such as formin, cystamin, hexamin, etc. These products are identical with hexamethylenamin and show no variations from it in chemical or pharmacologic reaction.

Helmitol, the methylene citrate of hexamethylenamin, also responds like the pure drug. There is this difference, however. When hexamethylenamin is dissolved in water no free formaldehyd is formed; when helmitol is dissolved in water a considerable amount of free formaldehyd is liberated. Formaldehyd, however, when taken by the mouth, is not excreted through the kidneys. When helmitol is taken, its excretion is identical with that of hexamethylenamin, i. e., in some cases, there is free formaldehyd liberated, and in others, none.

#### COMBINATION OF DRUGS WITH HEXAMETHYLENAMIN

In the hope that the presence of some other substance in the urine would cause decomposition of the hexamethylenamin, a great variety of substances have been given with it. Among these are potassium citrate, potassium iodid, sodium benzoate, salol, oil of wintergreen, etc. The results have not been encouraging, in no instance has the combination been more effective than the pure drug.

#### OTHER FORMALDEHYD-CONTAINING DRUGS

Dr. H. A. B. Dunning has furnished me with a number of formaldehyd compounds, some of them new ones, some of them have been excreted through the kidneys as in the case of a compound between formaldehyd and phenolsulphonephthalein. None, however, has shown a tendency to break down, liberating free formaldehyd. This phase of the subject is still under investigation.



## EXPERIMENTAL STUDIES WITH RABBITS

The use of hexamethylenamin in rabbits was carried out in order to determine its toxicity and its method of excretion. Only three animals were employed. The results obtained were identical. In the rabbit, hexamethylenamin is excreted primarily and principally through the kidneys. It is excreted unchanged, and is not broken down into formaldehyd. In small doses of from 2 to 5 grains, hypodermically, in a 2-pound rabbit, the excretion is practically entirely through the kidneys. When from 30 to 100 grains are given at a dose the principal excretion is through the kidneys but there is a large excretion through the bile. The drug is eliminated as hexamethylenamin, there being no formaldehyd liberated. The hexamethylenamin does not seem in the least toxic to the rabbit.

When a rabbit is given 30 grains of the drug hypodermically and then killed within an hour the findings in the different tissues are as follows: Urine, large amount, bile, considerable amount, cerebrospinal system, traces, blood, considerable amount, spleen, liver and kidneys, considerable amount, muscles, trace, skin, trace, in no tissue was any free formaldehyd found. These findings in the tissues and body fluids of the rabbit suggested the examination of some of the fluids of the human being where the drug has been thought to act efficiently.

## EXAMINATION OF THE BILE

I examined in all ten patients with biliary fistula. None of them were getting less than 60 grains a day, and in one case I gave 100 grains at a dose and collected the bile for twelve hours. The bile in every case was treated identically, i. e., it was diluted slightly with distilled water, acidulated with sulphuric acid, and distilled. In every case the distillate gave a clear formaldehyd reaction with Hehner's test. In not one could a trace be found by the test which I have employed.

As a control, I put a solution of 1 to 50,000 hexamethylenamin into bile, allowed it to stand an hour and then distilled. The presence of formaldehyd was easily determined and there seemed to be an actual concentration in the distillate.

## EXAMINATIONS OF THE SPUTUM AND SALIVA

In five healthy people I gave hexamethylenamin in 30-grain doses, at the rate of 120 grains a day for twenty-four hours, and then examined the saliva. By the Hehner test, either hexamethylenamin or formaldehyd was found to be present. By the phenolhydrazin-sodium-nitroprussid test, neither could be detected.

In three cases of bronchitis with mucopurulent expectoration, exactly similar technic was followed with identical results. By my test there was no free formaldehyd, and heating and acidulating proved that there was no free hexamethylenamin in amount sufficient to give the reaction.

#### EXAMINATION OF THE CEREBROSPINAL FLUID

The cerebrospinal fluid was examined in one case through the courtesy of Dr. Morse, of the Johns Hopkins Hospital staff. The patient, James B. D., aged 45, had normal temperature and no cerebral or spinal symptoms. For purposes of diagnosis, some of his cerebrospinal fluid was desired. Before the puncture he had been given, for twenty-four hours, 15 grains of hexamethylenamin every three hours. I obtained about 4 c c of clear fluid which showed a positive reaction with Hehner's test, but none whatever with the other test, even when boiled and acidulated.

#### CONCLUSIONS

These examinations of the bile, sputum, saliva and cerebrospinal fluid show that even after rather large doses of hexamethylenamin, there appears in them but traces of the drug, certainly in percentages less than 1 to 150,000. Whether this trace is of hexamethylenamin, as seems most likely, or of formaldehyd, it is impossible to state, because the only test which would show it is Hehner's which does not differentiate these two substances. So far as any therapeutic value is concerned, it does not make any difference because, as already shown, solutions of formaldehyd of the weakness indicated, do not possess any antiseptic value. I believe, therefore, that the use of hexamethylenamin for the curing or bettering of, or as a prophylactic against, infections of the bile passages, respiratory passages and cerebrospinal system is illusory, and cannot possibly yield results. I have no explanation to offer for the reported clinical and bacteriologic improvements, for with the exception of the urine, I have not tested this side of the question. In the urine the clinical and bacteriologic findings have conformed in every way with the chemical findings, viz., only those patients who show free formaldehyd have been improved by the drug.

The phenolhydrazin-nitroprussid test is very simple, and when applied gives the physician an easy method of determining the dose of hexamethylenamin which he should use, and also shows those cases in which no results from this drug can be expected.

The test is of value in determining the efficiency of compounds whose value rests on the liberation of free formaldehyd, and it is to be hoped that an endeavor will be successful in securing a substance which, when taken by the mouth, will be excreted through the kidneys and will liberate formaldehyd in the urine in every case.

Although it has its limitations, these experiences show that hexamethylenamin, when properly given, in more than a half the cases of urinary infection is of immense value, and at the present time superior to any other drug in common use

Finally, I want to express my gratitude for the enthusiastic support and many valuable suggestions given me by Dr Howard A Kelly during the progress of this work

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# COMPLETE AND PERMANENT HEART-BLOCK FOLLOWING THE USE OF DIGITALIS IN AURICULAR FIBRILLATION

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One of the commonest, as well as one of the most interesting, varieties of cardiac irregularity is that known as auricular fibrillation. In this condition the auricles, instead of contracting rhythmically, are thrown into a state of tremulousness involving small bundles of fibrils.

The walls of the auricle stand in the diastolic position, systole, either complete or partial, is never accomplished, the wall, as a whole, is stationary, but careful examination of the muscle reveals an extremely active condition, it appears to be alive with movement, rapid, minute and constant twitchings or undulatory movements are observed in a multitude of small areas upon its surface (Lewis).

The result, usually, is a rapid and extremely irregular pulse. From the turmoil in the auricles a shower of impulses passes down the bundle of His into the ventricles. The weakest of these impulses fail to affect the ventricles. The stronger ones, occurring at irregular intervals, cause ventricular systole and lead to the production of what used to be known as the *pulsus irregularis perpetuus* (Hering) or *arrhythmia perpetua* (Gerhardt). These terms are not accurate since the condition is occasionally compatible with a regular pulse and, while usually permanent, may be transient (Mackenzie, Hewlett and Barringer, Fox and others).

The venous pulse, in these cases, is characteristic and from it the diagnosis can readily be made. The *a* wave disappears entirely from the jugular sphygmogram and the same is true of the esophageal tracing (Hewlett) and the electrocardiogram (Hering). Whenever the diastole is somewhat prolonged, a series of fine wavelets may often be seen in the venous sphygmogram (Figs 5 and 6). Mackenzie was at first inclined to consider these as artefacts, but since they correspond in their rate with similar waves in the electrocardiogram, he now agrees with most other observers that there is reason to suppose them an expression of the auricular tremor.

While in most cases of auricular fibrillation, the pulse is rapid and irregular, it need be neither. In his classical monograph on Nodal Bradycardia, Mackenzie has reported a considerable number of cases of this sort

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in some of which the pulse was slow and irregular, in others slow and regular. Gibson, Lewis and others have reported similar cases. A seductive theory, in explanation of this phenomenon, has been advanced by Lewis. He considers the occurrence of a slow pulse in auricular fibrillation to be an expression of an impaired conductivity on the part of the auriculo-ventricular bundle. If the heart-block is partial, an occasional tremor only goes through and causes ventricular systole. The result is a slow and irregular pulse, sometimes with long pauses. If the block is complete, the fibrillating auricles can no longer affect the ventricles. The latter establish their own rhythm and beat slowly and regularly as in an ordinary case of complete heart-block. From the nature of the case, the validity of this explanation cannot be established in every instance. But, as Lewis has pointed out, one at least of Mackenzie's cases strongly supports this view. The patient, a subject of rheumatic fever, was known to have had impairment of conductivity, in greater or lesser degree, for twelve years. He then suddenly developed slow and irregular action of the heart, with evidence of auricular fibrillation. This lasted a week at the end of which time both auricles and ventricles again resumed their rhythmic action, but with an *a-v* interval twice as long as normal. Several months later the slow and irregular pulse, with auricular fibrillation, returned and thereafter persisted. Gibson has reported an equally instructive case. The first tracings obtained were those of ordinary partial heart-block, with an auricular rate of 168 and a ventricular of 42. On one occasion auricular fibrillation set in, with an irregular but still phenomenally slow pulse. A post-mortem examination revealed an increase in the fibrous tissue of the *a-v* bundle with wide separation of the fibers composing it. Lewis and Mack have reported a case of auricular fibrillation in which the ventricles beat regularly at a rate of 30 per minute. By means of the electrocardiograph they showed that the impulses from the fibrillating auricles were not transmitted to the ventricles and that the impulses originating the rhythm of the latter started at a point in the ventricular wall not far removed from the auriculo-ventricular ring. There is thus good reason to suppose that the slow pulse occasionally seen in auricular fibrillation is due to partial or complete heart-block, as the case may be.

Mackenzie has shown that digitalis slows the pulse far more readily and to a far greater extent in auricular fibrillation than in any other cardiac condition, with the exception of cases of partial heart-block. This phenomenon can readily be observed by anyone who studies this condition. Lewis was the first to suggest the theory that here, too, the slowing produced by the administration of digitalis is due to the production by this drug of a partial or complete heart-block, thus preventing the passage of some or all of the fibrillation impulses at the *a-v* junction.

It is well-known that digitalis, either through the vagus or directly or both, often depresses the conductivity of the bundle of His. This is especially the case where the conductivity of the bundle has already been impaired by some organic lesion. Thus cases of partial heart-block are nearly always aggravated by digitalis and the case of Windle, in which heart-block was apparently produced *de novo* by the administration of digitalis, was one of rheumatic mitral disease, in which an impairment of the conductivity of the bundle is not infrequently found. Similarly Mackenzie has shown that of cases of auricular fibrillation, those which are of rheumatic origin or those in which mitral stenosis is present, are most susceptible to digitalis. It is therefore reasonable to suppose, that in these cases we have, besides the auricular fibrillation, a pre-existing impairment of conductivity and that digitalis here produces its exceptionally great retardation of the pulse by still further depressing the conductivity of the already organically diseased bundle. Further clinical and, if possible, experimental evidence is needed to prove the validity of this theory in all cases. It is believed that the second case, to be reported below, may be of value in this connection.

In all cases hitherto reported, in which digitalis has slowed the pulse in auricular fibrillation, the action of the drug has been temporary. Even when the slow, regular pulse of complete heart-block has been produced, a discontinuance of the drug has been followed by a return of the rapid, irregular pulse characteristic of uninfluenced auricular fibrillation. That this need not always be the case, it is the object of this communication to show. It would seem, from the two cases to be related below, that occasionally the depression produced by digitalis in the conductivity of the diseased bundle may result in a permanent injury to the latter, leading to the production of a complete and permanent heart-block with its characteristic regular and extremely slow pulse. They further seem to show that this is an eminently undesirable accident, since in both patients the condition, after the establishment of the complete block, was far worse than before and death ensued in ten and sixty-four days, respectively.

CASE 1—Male, aged 80 years. No rheumatism, syphilis or alcoholism. In 1868 while suffering from a severe laryngitis, he had a sudden attack of syncope in which he thought he was dying. He felt well the next day, but soon after began to have periods of dyspnea on slight exertion which slowly grew more frequent and more severe. He did not consult a physician but twenty years later they had become so harassing coming on once a month or oftener and lasting several days that he retired from business. Since 1906 he had been more or less of an invalid—weak dyspneic with periods of cardiac palpitation and occasional precordial pain. His feet and legs became edematous and continued so until I saw him in 1908. I found him with an enormously dilated heart mitral and aortic regurgitation, marked arteriosclerosis congested and ptotic liver great edema of legs rapid and irregular pulse, urine scanty with albumin and casts. The usual treatment led to a gradual amelioration of his symptoms. Every few months thereafter he had a relapse which always yielded promptly to digitalis.

In April, 1910, I began to study his pulse with the Jaquet cardio sphygmograph, which showed the condition to be one of auricular fibrillation. On June 21, having been without medication for some time his pulse was irregular averaging 70 beats per minute with occasional bigeminy and with the jugular pulse of auricular fibrillation (Fig 1). Under digitalis (digitalis leaf tincture), his pulse became very slow (38 per minute) and nearly regular (Fig 2) without subjective improvement. The digitalis was discontinued but the heart block pulse persisted (Fig 3) dropping to 33 beats per minute on July 5, and continuing unchanged until his sudden death on July 8. An autopsy was refused.

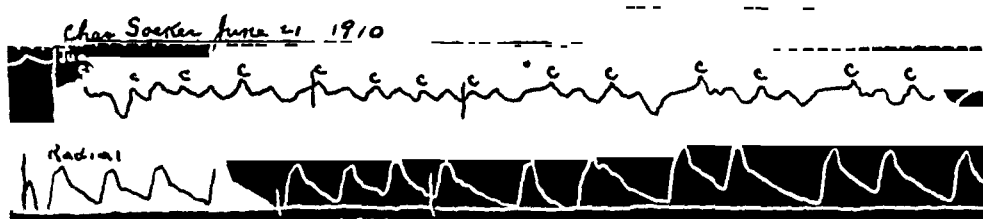


Fig 1—Jugular and radial pulse showing auricular fibrillation uninfluenced by digitalis

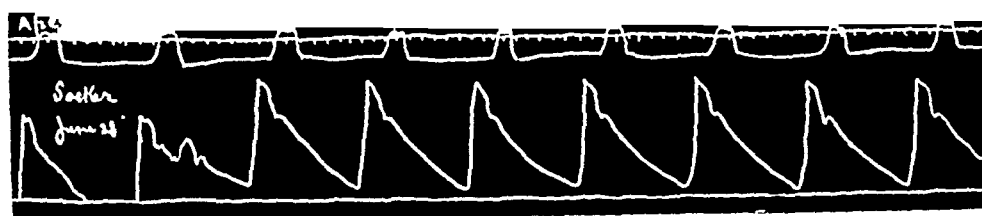


Fig 2—Apex beat and radial pulse after a week of digitalis. Note typical heart block pulse. The irregularity in the second pulse beat is due to a movement of the patient's hand.



Fig 3—Jugular and radial tracing, one week after digitalis was discontinued. The jugular pulse shows auricular fibrillation, the radial complete heart block.

We have here, then, a case of auricular fibrillation in which a moderate dose of digitalis produced complete auriculo-ventricular block, the latter persisting until the patient died, ten days after the discontinuance of the digitalis.

CASE 2—Male, aged 58 years, was admitted to the Washington University Hospital, service of Dr. George Dock, on Dec. 8, 1911. Besides the usual diseases of childhood he had had pneumonia at the age of 28 years and meningitis at 49 years. There was no history of rheumatism or of syphilis, but a definite one of long continued alcoholism. In June 1910 he was severely injured about the head. The accident was followed by a series of convulsions, very suggestive of

epilepsy and recurring at irregular intervals up to the time of his death nearly two years later. During some of these he bit his tongue and otherwise injured himself. In October, 1910, he first noticed evidence of cardiac incompetence—dyspnea and cardiac palpitation varying in intensity, but on the whole growing steadily worse until he entered the hospital on December 8, 1911. At this time the heart was found moderately enlarged, with evidence of dilatation of the left auricle and very irregular action. A low-pitched murmur was audible over the apex, beginning just after the second sound and occupying the first portion of diastole. When the latter was long, a distinct interval of silence could be made out between the end of the murmur and the beginning of the first sound. There was some pulmonary edema but none of the feet. The liver was not enlarged. The maximal blood pressure varied from 110 to 140 mm Hg according to the strength of the individual cardiac contractions, the minimal pressure being about 90 mm. The jugular and radial tracings showed the presence of auricular fibrillation (Fig 4), confirming the evidence of the murmur which was identical with that described by Mackenzie as characteristic of mitral stenosis when coexisting with auricular fibrillation.

Digitalis was given, at first tentatively but later, when this seemed ineffective, in doses of 1 cc of the tincture every four hours. No marked effect was produced until eight doses had been given. Then, at midnight, the resident, Dr Brotherhood, was called as the patient was in convulsions. He found the pulse 40 beats per minute with long periods of asystole and ordered the digitalis discontinued.

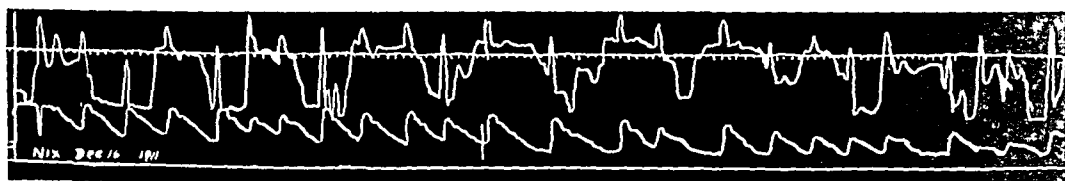


Fig 4—Jugular and radial pulse uninfluenced by digitalis. Auricular fibrillation.

The next day the patient seemed weak but was not carefully observed. On the following day, however, he went from one convulsion into another, each lasting a minute or two, apparently accompanied by hallucinations and followed by a brief period of confusion. There was no dyspnea or cyanosis. The pulse was very slow but strong with frequent intermissions, sometimes lasting several seconds, and very suggestive of heart-block (Fig 5, 6 and 7). It sometimes seemed as though a seizure were preceded by an unusually long intermission but of this I was not quite sure. It was impossible to feel or record the pulse during an attack on account of the violence of his motions. The cardiac outlines and sounds did not differ from those previously recorded. Atropin sulphate gr 1/60 hypodermically produced no effect on the pulse. This same day (December 20) the patient was taken home where I saw him thereafter at frequent intervals. On December 20 the pulse was nearly regular, 20 beats per minute still with the jugular pulse of auricular fibrillation (Fig 8). On the following day the pulse became entirely regular and from this time until his death on February 23 the cardiac condition was unchanged.

The pulse remained very slow, varying between 30 and 40 beats per minute, entirely regular except for rare extra-systoles. Many tracings were taken from time to time of which two are here reproduced (Figs 9 and 10). The cardiac dulness and the murmur remained unchanged. From week to week the dyspnea increased but there was never any evident cyanosis. The convulsions came on frequently and at irregular intervals the latter sometimes being a week or more in duration. No difference in the pulse could be noted between the convulsive and non convulsive periods. Frequent attempts were made to influence the pulse by



swallowing, pressure on the vagi, large doses of atropin and of digitalis but no effect could ever be noted. The blood pressure remained of the heart block type, the maximal pressure averaging 195 mm Hg, the minimal 60 mm. On February 23 he died, with no change in his condition except a progressive weakness and dyspnea. Until a minute or two before his death that is as long as the pulse could be felt it maintained its slow regular rhythm. An autopsy was performed a few hours after death, by Dr. George M. Smith of the pathologic department of Washington University.



Fig. 5



Fig. 6

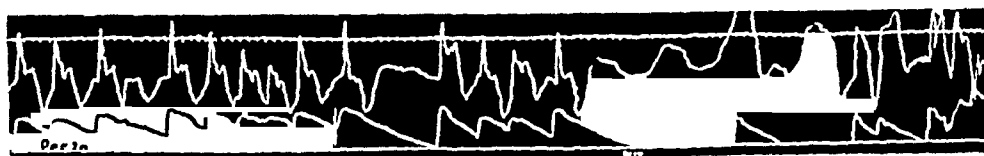


Fig. 7

Figs. 5, 6 and 7—Jugular and radial pulse 24 hours after digitalis was discontinued. Auricular fibrillation. The occasional long pauses between beats are suggestive of partial heart block. In Fig. 7 two respirations are recorded in the jugular pulse during a period of systole. During this and the following diastole the blood pressure fell so greatly that the collapsing radial allowed the writing point to leave the paper.

The following is an abstract of the pathologic findings, a more detailed account of which will appear elsewhere.

*Anatomical Diagnosis*—Valvular disease of the heart, mitral stenosis, fibrous myocarditis. General arterial sclerosis, calcification of part of ventricular septum causing destruction of auriculoventricular bundle, edema of lungs, chronic pleuritis (right), chronic passive congestion of lungs, liver, spleen and kidney, ascites, porencephalus.

Two small cysts, probably caused by old hemorrhages, were found at base of the occipital lobes. Brain otherwise was normal. Sections from the cortex of the motor area showed no changes.

Weight of heart 317 grams. Moderate hypertrophy of both ventricles. Dilatation of both auricles. Thrombus was found in the wall of the left auricle. Both mitral leaflets were much thickened and produced a contraction of the mitral orifice so that this barely admitted the tip of the little finger. At the base of the

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aortic leaflet of the mitral valve there was a large irregular calcareous nodule extending over into the ventricular septum. This nodule met and probably destroyed the auriculo-ventricular bundle just anterior to the septum near the junction before the bifurcation of the bundle had occurred. The microscopic examination of the node exhibiting the maximum point of injury showed that merely a few muscle fibers still remained. The node of Keith and Flack contained a considerable amount of fibrous tissue.



Fig 8—The pulse has become comparatively regular and very slow, indicating nearly complete heart-block. As in all the tracings, the jugular pulse shows that the auricle is fibrillating.

This case presents several points of interest. Tracings 5, 6 and 7 clearly show the onset of partial heart-block following the administration of digitalis. Tracing 8 shows evidence of nearly complete heart block on the following day. This, as indicated by Tracings 9 and 10,

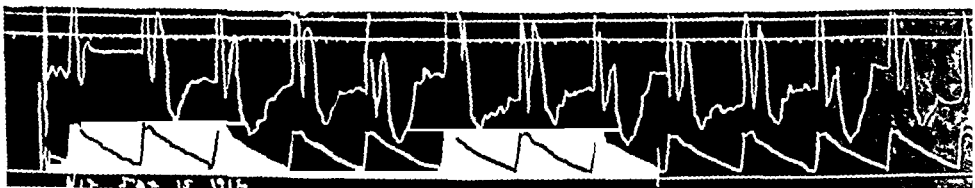


Fig 9



Fig 10

Figs 9 and 10—Two examples of nearly daily tracings taken between the onset of complete heart block on December 21 and death on February 2. They show continued auricular fibrillation in the jugular pulse and evidence of nearly complete heart block in the radial pulse.

complete and remained permanent. The fact that neither vagal stimulation nor atropin or digitalis affected the block, is evidence that the latter was not functional but organic, and this conclusion is borne out by the anatomic findings.

The conclusion thus seems justified that we had here a heart with an anatomically impaired auriculo-ventricular bundle but one still com-

its conductivity, administered the *coup de grâce* to the diseased bundle and led to its complete and permanent obliteration. It is possible, of course that the block was entirely due to the gradual extension of the anatomic lesion of the *a-v* bundle, which at this moment happened to interrupt its continuity, at first nearly and then quite completely, independently of the digitalis and that the administration of the latter was merely a coincidence. The fact however, that the phenomenon followed the use of digitalis in two cases renders this hypothesis less probable than the other.

Whether the patient's convulsions were due to the bradycardia remains problematic. Some of them were certainly epileptic and perhaps all of them were so. It may be that the cerebral anemia resulting from the block stimulated the brain to the production of an increased number of epileptic seizures.

It is a pleasant duty to thank my honored chief, Dr. George Dock, for permission to report this case and for the interest shown during its study.

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## THE ADRENAL GLANDS AND BLOOD-PRESSURE

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The first significant contribution to the function of the adrenal glands was made by Addison, when, in 1855, he discovered their relation to the disease which bears his name. Stimulated by this discovery, Brown-Séquard the following year succeeded in demonstrating that removal of both glands in an experimental animal leads to a marked asthenia of the muscular structures of the body such as characterizes Addison's disease. In 1895 Oliver and Shaefer showed that adrenal extract has a powerful effect on blood-pressure—a fact that was independently discovered by Czubski and Szymonowicz. It has since been shown that this effect is produced by extracts of the medullary portion of the gland only. It is shared, however, by extracts of chromaffin tissue wherever found.<sup>1</sup>

Probably the most significant discovery of recent years is that the injection of adrenal extract is exactly equivalent to stimulation of the sympathetic (thoracico-lumbar autonomic) nervous system. The result of such injection depends in any organ on its sympathetic innervation. If it has no sympathetic fibers no effect is produced. If such fibers are present the effect is stimulation or depression, depending on which function is mediated by these fibers. Finally, in an organ in which sympathetic impulses are infrequent the injection has correspondingly slight effect.<sup>2</sup> Recent researches at the Harvard Medical School<sup>3</sup> have shown that during periods of particular stress the adrenals are stimulated to an augmented secretion which reinforces the sympathetic activity characteristic of such periods. In cats under the influence of anger or fear partial asphyxia and strong sensory stimulation epinephrinemia has been demonstrated.

The idea very generally obtains that an important function of the chromaffin tissue is to maintain a constant tonic activity in the sympathetic system. Whether, however, such influence is mediated during periods of ordinary quiet existence is questionable. The theory is based largely on an assumption that minimal quantities of circulating epinephrin have an effect qualitatively similar to that of the comparatively

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\*From the Laboratory of Physiology of the Stirling Ohio Medical College

1 For an excellent detailed review of the literature on the adrenals see Vincent *Ergebn d Physiol* 1910 ix 509

2 Elliott *Jour Physiol* 1905 xxxii 401

3 Cannon and de la Paz *Am Jour Physiol* 1911 xxxiii 64 Cannon and Hoskins *Am Jour Physiol* 1911 xxx 274

enormous quantities that have usually been employed in experimental investigations. Such an assumption is not necessarily true. It is possible that the threshold of stimulation is sufficiently high not to be reached by the ordinary concentration of circulating epinephrin. That different quantities of epinephrin may have different effects is shown by the fact that in the small intestine a stimulating effect of epinephrin has been noted when very dilute solutions are used, whereas the effect of stronger solutions is depression.<sup>4</sup> A similar reversal of reaction has been noted recently by Stewart<sup>5</sup> when very dilute solutions are applied to uterine tissue.

In view of the fact that the sympathetic nervous system has an important regulatory influence in the so-called "vital functions," it is a question of considerable moment whether the adrenals actually do have the assumed tonic influence on this system. If so the vital activities must constantly fluctuate with variations in the activity of the glands. Any diagnosis, then, that fails to take them directly into account is to that extent inadequate. Similarly, if they have such an important function, every autopsy should include not only a careful microscopic examination of the glands but also a physiologic determination of the potency of their chromaffin tissue. If the tonic activity of the sympathetic system does depend on these organs their functioning must be a major factor in the physiologic regime as well as in many symptom complexes.

There is, however, as previously indicated, a possibility that the peculiar relationship subsisting between the chromaffin tissue and the sympathetic system is of utility only during periods of special stress. In that event there would ordinarily be no probable error introduced in diagnosis by a failure to consider the adrenals.

Of the bodily functions controlled by the sympathetics blood-pressure is supposedly one of the most sensitive to epinephrin. For this reason and on account of the ease with which blood-pressure can be recorded studies of the relation of the adrenals to the sympathetics can well be made on the vasomotor system. Possibly the two best known facts regarding the physiology of the adrenals are that their deficiency causes vascular hypotension, while, on the other hand, injection of epinephrin causes a marked hypertension. There are two possible factors in this hypertension—increased vasoconstriction and augmented heart beat. The latter factor is frequently masked by a cardiac inhibition mediated by the vagus nerve—a reflex reaction to the increased blood-pressure following vasoconstriction. It is not to be supposed, however, that the cardiac stimulation is in abeyance, a similar vasoconstriction without the

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4 Hoskins *Am Jour Physiol*, 1912, *xxv*, 363

5 Stewart *Jour Exp Med*, 1912, *xv*, 547

supporting epinephrin stimulus to the heart would lead to a considerably greater cardiac inhibition with correspondingly smaller elevation of pressure

#### EFFECTS OF EXPERIMENTAL ADRENAL DEFICIENCY

A condition of adrenal deficiency can be obtained experimentally by extirpating the glands or by occluding their circulation, these procedures give a condition of extreme, though not absolute, chromaffin deficiency. As to the ultimate effects of such experiments there is no question. Within a few hours to a few days there develops an asthenia which is shared by the musculature of the circulatory system and leads to extreme vascular hypotension. As to the immediate effects, however, the evidence is not concordant. A number of investigators have studied the effects of tying off the adrenal vessels while blood-pressure was being recorded. Stiehl and Weiss<sup>6</sup> noted in rabbits a fall of pressure immediately succeeding such ligation, followed by an immediate rise when the ligatures were released. But Young and Lehman,<sup>7</sup> performing the same experiment on dogs, observed on ligation but little fall, and that occurred very gradually. When the ligatures were released there followed, in three of their eight experiments, a decided rise of pressure, in two, a slight rise and in three, no effect. Young,<sup>8</sup> who subsequently repeated the work, observed no significant fall of pressure for hours after tying off the glands. Similar negative results have been obtained by Kahn<sup>9</sup> in rabbits and by Hoskins and McClure<sup>10</sup> in dogs.

That circulating epinephrin is quickly destroyed is well known. If therefore, the adrenals by their secretion exert a constant tonic influence on the sympathetic system, ligating off the glands should result in an immediate fall of pressure. The failure of such a result militates against the view that a tonic influence exists. It is to be noted that in such experiments the effects of making the occlusions alone are significant. Whether or not a subsequent rise occurs when the vessels are released, means little. Checking the circulation in any given case might result either in a long continued depression of the glands such as occurs in the kidney after occlusion of the renal vein, or in an accumulation of elaborated secretion. Consequently, releasing the vessels would not be at all likely to restore normal conditions and any effect produced would not be intelligible.

6 Stiehl and Weiss. *Arch f d ges Physiol* 1901, LXXXI, 107

7 Young and Lehman. *Jour Physiol*, 1908, XXXIII p. 13

8 Young. Cited by Vincent (Note 1)

9 Kahn. *Arch f d ges Physiol* 1911 cxl, 216

10 Hoskins and McClure. *Am Jour Physiol* 1912 LXX 192

## EFFECTS OF INJECTING EPINEPHRIN

Another method of investigating the relation of the adrenals to blood-pressure is to determine at what rate epinephrin must be injected into the blood-stream of an animal to cause a minimal rise of pressure and compare this with the actual rate of secretion by the adrenal glands. Very little work apparently has been done along this line but Lewandowski has observed that the injection into an experimental animal of blood from the adrenal veins at the rate at which it normally flows has no effect on blood-pressure.<sup>11</sup> The proposed plan of procedure at once raises several questions. What is the concentration of epinephrin in the blood in the adrenal veins?<sup>2</sup> What is the rate of blood-flow in these veins?<sup>2</sup> Is there normally an accumulation of epinephrin in the blood-stream sufficient to maintain a concentration above the threshold value for sympathetic stimulation?<sup>2</sup>

As to the concentration of epinephrin in adrenal blood Ehlmann,<sup>11</sup> using the enucleated frogs eye as a test object found in the rabbit a value of 1:1 000,000 to 1:10 000 000. Watterman and Smit<sup>12</sup> however having noted that fresh serum causes mydriasis independent of its epinephrin content thought Ehlmann's values too high. Making similar determinations after keeping the serum for twenty-four hours on ice they found a mydriasis corresponding to that of an epinephrin solution of 1:10 000 000. This they regarded as the normal concentration. More recently O'Connor<sup>13</sup> with better technic using Tiendelenburg's frog perfusion method has found epinephrin in plasma from the rabbit's adrenal veins in concentration of 1:1 000 000 to 1:5 000,000. Stewart<sup>15</sup> has recently reported an instance in which he was unable to detect epinephrin in the adrenal blood of a dog.

In order to avoid as far as possible abnormal experimental conditions we attempted first to determine in the dog somewhat indirectly the adrenal output. Cannon and de la Paz have described a method of obtaining samples of blood by inserting a flexible catheter through the femoral vein into the vena cava to the adrenal region. We hoped to be able to demonstrate in blood so collected an epinephrin content enough higher than that of ordinary venous blood to permit a determination of the difference. Then by allowing for subsequent dilution in the heart and considering the rate of general blood-flow we might calculate the rate of epinephrin secretion. But the quantity secreted proved too minute for detection by the rabbit intestine method (described below) which was used. It was proved, however, that there is a difference of less than 1:100,000,000 in the epinephrin content of blood from the vena cava at

11 Ehlmann Arch f Exper Path u Pharm 1905 iv, 39

12 Watterman and Smit Arch f d ges Physiol, 1908, cxviii, 198

13 O'Connor Arch f exper Path u Pharm 1910 lxi, 161

the mouths of the lumbo-adrenal veins and that from the femoral vein. These results indicate roughly that there is in the arterial blood as it leaves the heart at most, less than one part of epinephrin in 200,000,000.

Being unsuccessful in these attempts, we then made a number of direct determinations of the epinephrin content of the blood from the lumbo-adrenal veins. The blood was collected by a method that has been used by a number of other investigators. The animals were etherized, then, while the viscera were protected by warm towels, the vena cava and

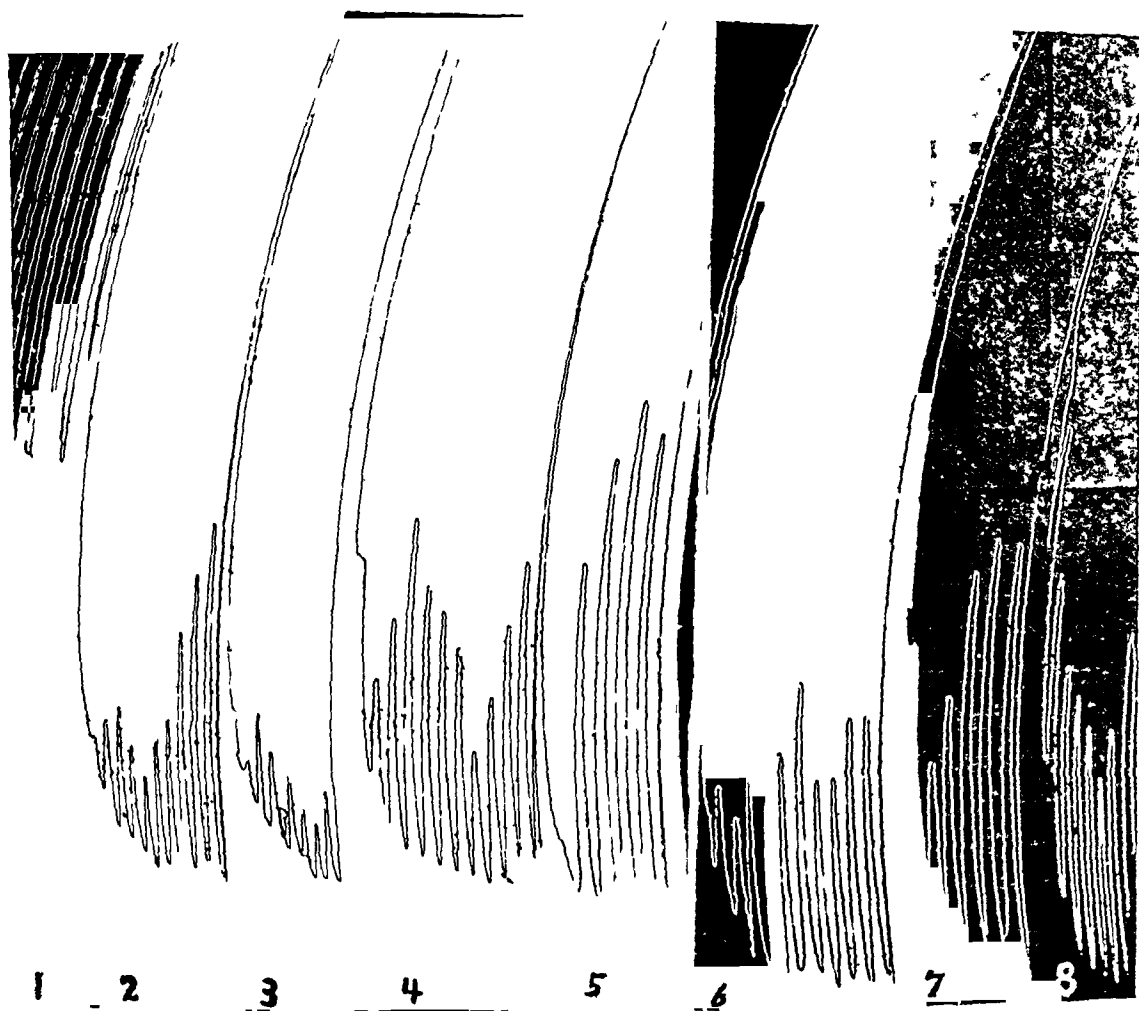


Fig 1—Epinephrin content of blood from adrenal veins. Segment of rabbit intestine beating in. 1 Blood from femoral vein. 2 Blood from adrenal vein. 3 Adrenalin 1:4,000,000. 4 Blood from adrenal vein. 5 Adrenalin 1:8,000,000. 6 Adrenalin 1:6,000,000. 7 Adrenalin 1:7,000,000. 8 Blood from adrenal vein. Blood diluted four times. Adrenalin solutions in blood from femoral vein similarly diluted.

aorta were ligated posterior to the renal veins, the renal veins were ligated at the hilus of each kidney. Then an oiled right angle glass cannula was inserted into one renal vein so as to drain the vena cava, which was finally occluded by a hemostat anterior to the mouths of the lumbo-adrenal veins. Care was taken to avoid massaging the adrenal gland-



The blood that had collected during the final stages of the procedure was carefully pressed out through the cannula, which was then elevated a few centimeters to simulate normal pressure. After the vena cava had refilled and blood-flow was reestablished through the cannula a three-minutes sample was taken for tests. Previous to this about 25 cc of blood was withdrawn from the femoral vein to serve as a "standard." The blood in each case was defibrinated by beating as it flowed.

TABLE 1—Output of Epinephrin from Adrenal Glands of Dogs

Dog	Weight, Kilos	Rate of Blood Flow cc per Minute	Epinephrin Content	Output per Dog per Minute*	Output per Kilo per Minute*
A	10.0	8.0	1 2500 000	3.0	0.3
B	5.2	3.0	1 2000 000	1.5	0.3
C	15.0	16.0	1 1500 000	3.5	0.23
D	13.1	21.0	1 1000 000	5.0	0.37
E	13.5	13.0	1 8000 000	1.5	0.8
Aver	11.1	12.2	1 1200 000	2.5	0.25

\*The figures in this column represent cc of 1 1,000,000 solution

To determine the epinephrin content we employed the rabbit intestine method as previously described by Hoskins<sup>14</sup>. The method in brief, consists of applying the blood to be tested to a segment of rabbit intestine rhythmically beating in defibrinated blood from the femoral vein. A depression of the tonus and the rhythmic activity of the segment occurs proportional to the quantity of epinephrin present. The segment used is "calibrated" in each instance by noting the effects of known concentrations of epinephrin in the "standard" blood. In the use of the intestine method better results are usually obtained if the blood is diluted two to four times. In ordinary blood there is a stimulating substance that may act so strongly as seriously to interfere with the reaction to epinephrin. In the experiments herein reported "adrenalin" (Parke, Davis & Co.) was used as standard epinephrin.

In such experiments, incidentally, blood must always be used as standard. Much confusion in the literature has arisen from attempts to compare blood-serum or plasma with standard saline solutions of epinephrin, thereby ignoring the possible influence on the test tissues of the blood itself—effects which in every case are significant<sup>13, 14, 15</sup>.

14 Hoskins Jour Pharm and Exper Therap, 1911, iii, 93

15 Stewart Jour Exper Med, 1911, xiv, 377 Kahn Munchen med Wehnsch, 1912, No 13

In Table 1 is summarized the results of our determinations of the epinephrin content of the "adrenal" blood. The proportions varied from approximately 1 2,000,000 to 1 8,000,000, with an average of 1 4,200,000. Figure 1 shows the tracings from which the estimation in case of Dog "B" was made. Our results as they stand are in satisfactory agreement with those of previous investigators. In common with those results however, they involve two sources of experimental error. The blood was obtained under abnormal pressure conditions, and was necessarily collected during strong sensory stimulation incident to visceral exposure and operative trauma. The effects of abnormal pressure conditions are problematic, but strong sensory stimulation has been shown to result in excessive epinephrin secretion. It is altogether likely, therefore, that the estimated epinephrin content of the adrenal blood is higher than obtains under normal conditions.

Determinations of the rate of blood flow in the adrenal veins apparently have not been made.<sup>16</sup> In Table 1 is included the rate at which the blood was collected in our experiments. It averaged 12.2 c.c. per minute. This rate probably only roughly approximates that under normal conditions. We found an average output of epinephrin of approximately 2.5 c.c. 1 1,000,000 solution per minute, or 0.25 c.c. per kilo per minute. O'Connor,<sup>13</sup> using the same method of collecting the blood, has found in the rabbit an average flow of approximately 0.5 c.c. per minute. The concentration of epinephrin averaged about 1 2,500,000. The epinephrin output, then, would be equivalent to about 0.2 c.c. 1 1,000,000 solution per minute.

An indirect method of determining the epinephrin output suggested itself, a method which would obviate the abnormal conditions previously mentioned. We had noted that a certain amount of adrenalin can be injected into a femoral vein without producing any effect on blood-pressure. This fact can be interpreted in two ways: either the normal output from the animal's own adrenals is below the threshold value necessary to affect pressure, or the vasomotor system is not sensitive to variations in the quantity of circulating epinephrin of the magnitude used. By direct experiment it was found that differing effects were produced by variations in the quantity injected which were decidedly smaller than the amount required to produce an initial effect. Figure 2 for instance shows the results of injecting varying quantities of 1 500,000 epinephrin solution into the femoral vein while recording carotid pressure. The dog was sensitive to variations of 0.1 c.c. whereas 0.4 c.c. was required to produce an initial effect. Such results indicate that the quantity of epinephrin normally circulating is not sufficient to affect the vasomotor system.

<sup>16</sup> Burton-Oritz. Personal Communication. 1912.

It appeared then, that a comparison of the amount of epinephrin necessarily injected while the adrenals were intact to raise to an effective value the epinephrin content of the circulating blood with the quantity necessary after occlusion of the adrenal vessels would show more or less accurately the quantity produced by the glands themselves.

Proceeding on this assumption we made the determinations summarized in Table 2. While carotid blood-pressure was being recorded on a slow extension kymograph adrenalin solution was injected from a buret connected with a cannula in the femoral vein. Thus normal epinephrin discharge was simulated. The buret was graduated to tenths of a cubic centimeter. The rate of outflow was regulated by an ordinary glass stop-cock. Adrenalin in Ringer's solution of 1:100,000 to 1:500,000 was employed as the conditions of each case required. For the more sensitive animals of course the higher dilution was used. The purpose was

TABLE 2.—AMOUNT OF EPINEPHRIN REQUIRED FOR MINIMAL EFFECT ON BLOOD PRESSURE BEFORE AND AFTER REMOVAL OF ADRENALS

Dog	Weight Kilos	Minimal Quantity Required Before Removal of Glands		Minimal Quantity Required After Removal of Glands		Difference, Adrenal Output	
		Per Dog*	Per Kilo†	Per Dog*	Per Kilo*	Per Dog*	Per Kilo†
F	6	1.5	0.25	3	0.5	1.5	0.25
G	8	3	0.37	5	0.6	2	0.25
H	5.6	1	0.17	5.6	1.0	1.6	0.29
I	4.0	1.8	0.45	2.1	0.6	0.6	0.15
J	7.2	2.8	0.39	3.6	0.5	0.8	0.12
K	4.9	0.3	0.06	0.6	0.13	0.3	0.07
L	6.1	3	0.47	3	0.47	0.7	0
M	10	3.5	0.35	3.5	0.35	0.1	0
N	1.6	3.5	0.76	3.5	0.76	0.1	0
Av	6.3	2.6	0.42	3.1	0.55	0.75	0.13

\*The figures in this column represent cc. of 1:1,000,000 solution.  
†“0” = less than 0.1, the limit of sensitiveness of test.

to use a solution sufficiently concentrated to avoid the injection of significant quantities of fluid and sufficiently dilute to permit ready control of the rate of epinephrin injection. For convenience, the solutions are all expressed in the table as 1:1,000,000. The solution was freshly prepared in each instance just before use. Injections were made at various rates at short intervals until the minimal quantity necessary to affect pressure was determined. With such dilutions as were used, there was no impairment of sensitiveness during the experiment. Usually the injections were continued for thirty seconds. The experimental animals were etherized carefully to avoid excitement, and the cannulas were inserted with the

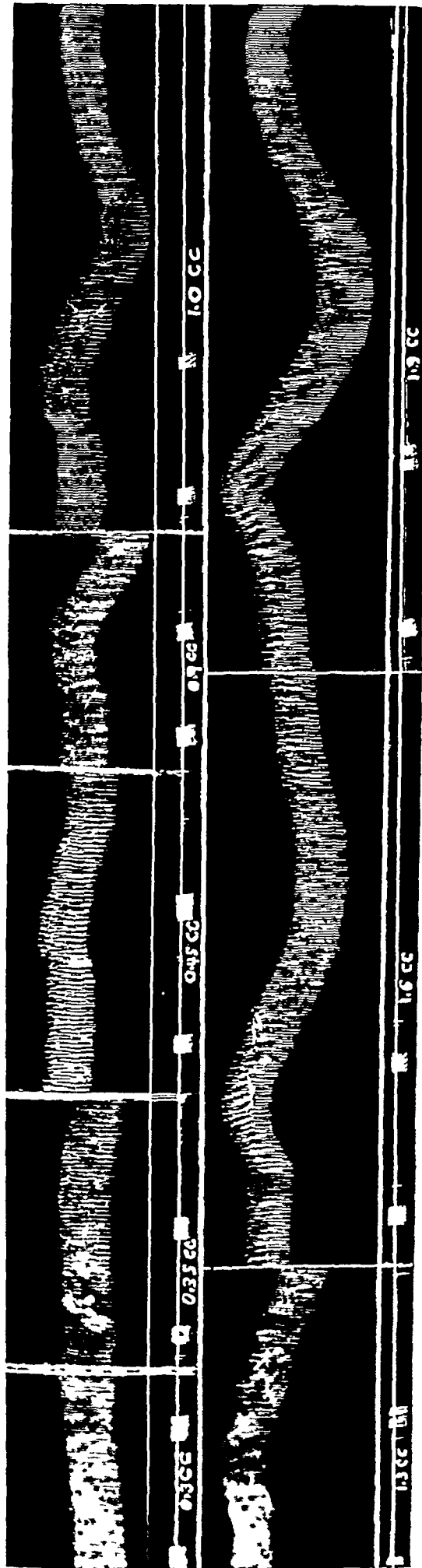


Fig. 2.—Effects of varying quantities of epinephrin on blood pressure. Pressure from carotid artery of dog. Adrenalin 1 500 000 in Ringer's solution injected into femoral vein. Injections continued 30 seconds. Time, 30 seconds, blood pressure, 120 mm. Quantities 0.3 cc to 1.0 cc. Injections begun at first wide mark on signal line and discontinued at second.

least feasible trauma to avoid sensory stimulation, both of which influences have been shown to cause augmented epinephrin discharge.<sup>3</sup> Uniform light anesthesia throughout the experiment was secured by causing the animal to breathe through a tracheal tube from a Wolf flask containing ether, by use of a short tube and small flask with large openings; dyspnea due to rebreathing was avoided.

After the first determination was made the abdomen was opened by a median incision and while the viscera were protected by warm towels an aneurysm needle carrying a double ligature was passed directly under each adrenal. Then the ligatures were brought up one to the mesial and one to the lateral side of each gland and securely tied. Thus each organ was completely isolated. Care was taken not to rupture the adrenal tissue and thus to liberate any elaborated secretion which might be resorbed and vitiate the remainder of the experiment. The abdomen was closed, and after a few minutes delay to permit the immediate effect of the operation to pass off a second series of injections was made and the minimal quantity required to affect pressure again determined.

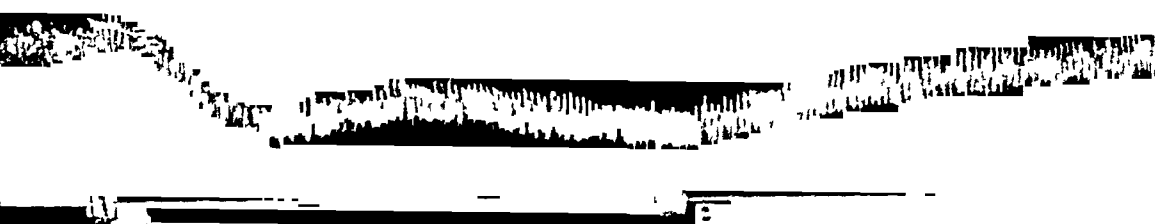


Fig. 3.—Record showing sustained vascular hypotension due to epinephrin from 1 b 0 8 c c 1 200 000 adrenalin in Ringer's solution (1 minute). Time, 30 seconds, pressure, 140 mm.

From Table 2 it appears that to affect pressure in the intact animal 0.42 c c per kilo of 1:1,000,000 epinephrin solution was required; after occlusion of the adrenal vessels 0.05 c c was required. Under fairly normal conditions, then, the adrenal glands had been producing as a maximum approximately 0.13 c c 1:1,000,000 solution of epinephrin per kilo per minute. These findings indicate that the direct determinations of Table 1 (0.25 c c per kilo per minute) were as supposed too high. These latter findings are probably also high in that no allowance was made for a possible impairment of sensitiveness of the vasomotor system from the shock incident to tying off the adrenals. Support for this hypothesis is found in the fact that as greater facility in performing the operation was acquired, the difference in quantity of epinephrin required to affect pressure became continuously smaller. The later experiments of the series indicate a very minute output.

The data of Table 2 answer the question as to the rate of injection necessary to affect the blood-pressure of an epinephrectomized animal. An average of 0.55 c c 1:1,000,000 adrenalin per kilo per minute was required. Both Tables 1 and 2 indicate that epinephrin is not secreted in quantity sufficient to produce such effect. Table 1 shows a production of 0.25 c c and Table 2, 0.13 c c per kilo per minute. The very fact, however, that epinephrin can be injected into the femoral vein of an intact animal without affecting pressure while the animal reacts differentially to variations of less magnitude than the quantity first injected, seems to obviate any real necessity for answering the question. The data of Table 2 alone justify a positive conclusion that the adrenals do not ordinarily produce sufficient epinephrin to stimulate the sympathetic system.

The term *affect* rather than *raise* pressure has up to this point been used advisedly. Early in the researches it appeared that epinephrin is not, as ordinarily assumed, primarily a *pressor* agent. The primary effect of epinephrin administered in doses gradually transcending ordinary physiologic limits is *depression*. Figures 2 and 3 show the characteristic effects of minimal quantities of adrenalin. The first effect to appear is a brief, inconsequential rise followed by a subnormal pressure and a gradual return to normal while the injection continues (not shown in tracings reproduced). If the dose is slightly larger the subnormal pressure persists until the adrenalin is discontinued. (See Fig. 3.) If the dose is slightly further increased a pressor effect appears that may exactly cancel the depressor effect and leave the pressure after the initial fluctuation at normal level. Finally, with a dose again increased a sustained hypertension may be obtained. Thus, in one typical instance in which the point was specifically under investigation, although the characteristic primary effect appeared with the injection of 3 c c of 1:1,000,000 solution of adrenalin per minute, it was not until 17 c c was used that a minimal sustained rise occurred. The depressor effect of small quantities of adrenal extract has been noted from time to time by previous investigators, but it has been ascribed to general "depressants" that occur in tissue extracts.<sup>1</sup> Such an explanation, however, cannot apply to the effects of a pure isolated epinephrin, such as was used in these experiments.

As a preliminary note, mention may be made that in a series of experiments now under way but not yet completed, considerable evidence has been accumulated which indicates that intestinal peristalsis is brought to a stand-still by quantities of epinephrin inadequate to exert a pressor influence. These results, so far as they go, seem to indicate conclusively that adrenal secretion cannot be a direct factor in the maintenance of blood-pressure. An organism obviously could not make use of a mechanism which, to be effective in other regards, would stop peristalsis.

## SUMMARY

1 Determinations by the rabbit intestine method indicate a difference in epinephrin content of the blood of dogs from the adrenal region of the vena cava, and that from the femoral vein of less than 1 100,000,000. This roughly indicates an epinephrin concentration in arterial blood of less than 1 200,000,000.

2 Similar determinations indicate an epinephrin content of blood from the lumbo-adrenal veins of 1 1 000,000 to 1 8,000,000, and an output of 0.25 cc 1 1 000 000 solution per kilo per minute. This value is probably higher than obtains under normal conditions on account of the sensory stimulation necessarily involved in collecting the blood.

3 Comparison of the amount of epinephrin required to affect blood-pressure with the adrenals intact with the quantity required after occlusion of the adrenal circulation indicates as a maximum an epinephrin secretion of 0.13 cc 1 1,000,000 solution per kilo per minute. This value is also probably too high.

4 The amount of epinephrin necessary to affect blood-pressure is on an average approximately 0.42 cc 1 1,000,000 solution per kilo per minute in the intact animal, and 0.55 cc after removing the adrenal glands.

5 The characteristic primary effect of epinephrin administered intravenously is lowering of blood-pressure.

6 The quantity required to cause minimal hypertension is several times this quantity, or at least ten to twenty times the amount secreted by the adrenal glands.

7 Incomplete data indicate that peristalsis is depressed by quantities of epinephrin inadequate to raise blood-pressure.

8 Adrenal secretion is not, therefore, a direct factor in the maintenance of the tonus of the vasomotor system.

9 It is probable, then, that other activities controlled by the sympathetic nervous system are not directly dependent on adrenal activity.

## DISCUSSION

Realizing the unfortunate profusion of speculative literature on internal secretion, it is with some hesitation that we venture to discuss further the functions of the adrenals. Attention may be called, however, to certain data that seem in this connection especially significant.

Addison's and Brown-Séquard's early work prove conclusively that the glands do in some way promote the nutrition of the muscular tissues. Biedl's later work, however, makes it appear probable that this function is mediated by the cortical portion of the gland<sup>1</sup>. Data now available scarcely permit any deductions as to how this function is brought about.

Particularly significant, also, seems Elliott's<sup>2</sup> observation that plain muscle deprived of its sympathetic innervation acquires an increased irritability to epinephrin. This fact strongly suggests that the chromaffin tissue has a function of compensating for injury of sympathetic fibers. Thus, after sympathetic impulses fail, their place is taken by epinephrin stimulation of the nerve-endings.

Recent researches on adrenal control carried on at the Harvard Medical School<sup>3</sup> in connection with such data as this paper affords, seem to indicate that chromaffin secretion is largely a reserve for times of special stress. Falta and Priestly<sup>17</sup> have recently shown that the injection of large doses of epinephrin leads to an unusual distribution of the blood in the body. If the organs of an animal under the influence of this substance are quickly tied off an excess of blood is found in the lungs, brain, liver and kidneys, while the skin, spleen, mucous membranes and muscles are pale. That epinephrin strongly inhibits the alimentary canal and stimulates the heart is well known. During muscular activity there is an increased blood-flow in the particular muscles involved, brought about by local vasodilator mechanisms. If these local mechanisms be efficient to overcome the general constricting effect of circulating epinephrin on the blood-vessels of the muscles, as they obviously must be, there would seem to be provided an arrangement to bring about an adaptive distribution of the blood favorable to extreme muscular effort. Thus, structures not involved would remain quiescent with a restricted blood-supply while the *active* muscles, the central nervous system and the eliminative organs would be extensively supplied. Also a reserve food-supply, the glycogen of the liver, would be freely available to prevent the hypoglycemia that would otherwise quickly ensue.

The Harvard researches,<sup>3</sup> in connection with Crile's<sup>18</sup> principle of "phylogenetic association," explain how this adaptive mechanism may be brought into play. During the racial history, anger, fear, or pain have commonly resulted in combat or flight, either of which makes special demands on the muscular system. Excessive activity in turn leads to a condition of partial asphyxia. This condition, as well as the antecedent emotion or pain, causes an augmented epinephrin discharge, which in turn brings about the reactions previously mentioned. The hypothesis derives additional support from the fact observed by Cannon, Shohl and Wright<sup>19</sup> that fear or anger in a quiescent animal actually does cause a condition of hyperglycemia. Macleod,<sup>20</sup> Edie, Moor and Roaf<sup>21</sup> and others have noted a similar reaction to asphyxia.

17 Falta and Priestly. Berl. klin. Wehnschr., 1911, No. 47.

18 Crile. Boston Med. and Surg. Jour., 1910, clxviii, 893.

19 Cannon, Shohl and Wright. Am. Jour. Physiol., 1911, xxix, 223.

20 Macleod. Am. Jour. Physiol., 1909, xxi, 302.

21 Edie, Moore and Roaf. Biochem. Jour., 1911, v, 325.



Finally, there is considerable evidence that the adrenals have important interrelations with other organs of internal secretion<sup>22</sup> Just what these relations specifically are, however, cannot yet be stated

The data of this paper justify further emphasis of a principle mentioned in a previous communication<sup>4</sup> Studies directed toward the elucidation of the physiology of the adrenal glands must be *quantitative* That the effects of epinephrin injection may vary qualitatively as well as quantitatively according to the amount used, is definitely proved The actual effect in any organ is the algebraic sum of the effects on the component tissues — tissues which may have varying thresholds of irritability and may be affected synergetically, or, as in case of the intestine,<sup>4</sup> antagonistically The total effect may vary diametrically, depending on the amount used Ignoring this fundamental principle of pharmacodynamics has led to many unjustified conclusions regarding adrenal functions In any case, before any deductions regarding ordinary adrenal physiology can be made from the effects of epinephrin injections, it must be shown that the quantities used are within physiologic limits

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<sup>22</sup> For a review of the literature see Hoskins, *Am Jour Med Sc*, 1911, cxli, (March and April)

# THE DIAGNOSTIC WORTH OF THE GLYCYLTRYPTOPHAN AND THE TRYPTOPHAN TESTS IN DISEASES OF THE STOMACH

A REPORT OF 1,175 CASES STUDIED BY A UNIFORM METHOD

FRANK SMITHIES, M D

ROCHESTER, MINN

The surgeon and the pathologist have shown that when cancer of the stomach is diagnosed early that affection is as amenable to treatment as is cancer in other parts of the gastro-intestinal tract. At present, it would seem that early diagnosis rests largely on microscopic examination of sections of extirpated tissue. Inasmuch as prognosis is directly dependent on the process at diagnosis it would appear desirable to elaborate certain diagnostic procedures that might anticipate laparotomy findings.

Recently the physiologic chemist has undertaken the investigation of biologic problems bearing on clinical medicine. Various workers, notably Muller,<sup>1</sup> Fischer,<sup>2</sup> and Abderhalden<sup>3</sup> have reported that malignant neoplasms contain certain peptidolytic enzymes. This discovery appeared to have clinical value when Neubauer and Fischer<sup>4</sup> announced that simple peptides, particularly the dipeptide, glycyltryptophan, were hydrolyzed by cancerous ferments. In the case of glycyltryptophan, the amino-acid, tryptophan, which is liberated by this cleavage, can be recognized readily in acid solution by the rose-pink color occurring on the addition of bromin. This reaction forms the basis of the "glycyltryptophan test" for cancer of the stomach, advanced by Neubauer and Fischer.

Clinicians generally have disagreed widely on the actual value of the test. The reaction's sponsors, together with Lyle and Kober<sup>5</sup> and Weinstein<sup>6</sup> early reported enthusiastically on the procedure. Later

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\*From the Laboratory of Gastro Enterology, St. Mary's Hospital Mayo clinic

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1 Muller Ztschr f klin Med, 1889, xvi, 496

2 Fischer Deutsch Arch f klin Med, 1902, lxxii, 415

3 Abderhalden Ztschr f physiol Chem, 1909, lxxii, 136

4 Neubauer and Fischer Deutsch Arch f klin Med 1909, xciii, 499

5 Lyle and Kober New York Med Jour 1910 xci 1151

6 Weinstein Jour Am Med Assn 1910 lx, 1085

observers, especially Warfield,<sup>7</sup> Oppenheim,<sup>8</sup> Kohlenberger<sup>9</sup> and, most recently, Sanford and Rosenbloom,<sup>10</sup> declare that the test is of dubious value. They admit that while certain cases of cancer of the stomach undoubtedly give the reaction, many non-malignant gastric disturbances give similar tests. Factors claimed to influence the reliability of the reaction are swallowed saliva, bacteria, bile or blood in the gastric extracts, low or absent free hydrochloric acid and regurgitated duodenal contents.

In October, 1911, Weinstein<sup>11</sup> announced that he had improved on the Neubauer and Fischer test. He stated that in extracts from cases of carcinoma ventriculi there exist free amino-acids, notably tryptophan, and that the latter can be tested for directly with bromin. This procedure appeared to render unnecessary the addition of glycyltryptophan to such gastric contents, with search for its cleavage products subsequently. This so-called "tryptophan test" was claimed as a reaction pathognomonic of cancer of the stomach. Weinstein did not, however, go so far as to state just how early in the progress of the disease this test could be regarded as pathognomonic. Certainly, in the clinical cases which he briefly quoted when the tryptophan test was positive, other evidences of cancer were not lacking. Recently Hall and Williamson<sup>12</sup> and Sanford and Rosenbloom<sup>10</sup> have recorded observations which appear to indicate that Weinstein's test has even less value than in their experience, had the glycyltryptophan test.

The great difference of opinion regarding the practical worth of the two tests mentioned led us to make the observations herewith submitted.

#### AUTHOR'S STUDY

From October 1, 1911 to May 15, 1912, the Ewald test breakfast was administered to 1,626 different individuals at St. Mary's Hospital (Mayo Clinic). On the gastric extracts from more than 1,400 of these patients, glycyltryptophan and tryptophan tests were made. On 1,175 different individuals, the gastric extracts were tested according to the modification of the glycyltryptophan and the tryptophan tests recently

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7 Warfield. Bull. Johns Hopkins Hosp., May, 1911, 150.

8 Oppenheim. Deutsch. Arch. f. klin. Med., 1910-11, ci, 293.

9 Kohlenberger. Deutsch. Arch. f. klin. Med., 1910, xciv, 148.

10 Sanford and Rosenbloom. THE ARCH. INT. MED., 1912, ix, 445.

11 Weinstein. Jour. Am. Med. Assn., 1911, lvi, 1420.

12 Hall and Williamson. Lancet, London, 1911, clxxi, 731.

suggested by me<sup>13</sup> This modification appears to have the advantages of requiring less of the test ingredients than the Neubauer and Fischer method, of being a controlled procedure, and one in which the end-reaction may be easily determined It is the purpose of this communication to report our experience with the cases tested by this uniform method

Certain precautions taken in the manipulation of the reaction might be mentioned briefly All glassware was boiled in distilled water and dried before using The solution of glycyltryptophan employed was obtained, in bulk and unopened, direct from the makers To guard against its tendency to crystallize out, in cold solution, the preparation was kept in a water-bath at 37 C until used All gastric extracts were carefully filtered before testing, and the tests were set up within two hours, at the outside, from the time the contents were taken from the

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13 The test is set up as follows

1 Test-tubes of 10 cc capacity are employed These should be carefully cleaned with boiling water and dried inside They are numerically marked for identification with a wax pencil Into each test-tube is carefully measured, by means of a sterile graduated pipet, 0.5 cc of the glycyltryptophan solution Five cc of the recently secured filtered gastric extract are then measured by a clean, graduated pipet and poured into the correspondingly numbered test-tubes to which glycyltryptophan solution has been already added Two control tubes are used In one is placed 0.5 cc of glycyltryptophan solution and 5 cc of normal salt solution, and into the other is placed 5 cc of normal salt solution, without added glycyltryptophan solution In the entire series, each tube next receives 0.5 cc of toluol (Toluene, Merck) The contents of the tubes are then mixed by inverting several times The tubes are next placed in a water-bath (an incubator may be used) at 37 C for twenty-four hours

2 At the expiration of the incubation period, the test-tubes are removed from the water-bath Clean test-tubes of 10 cc capacity and numbered to correspond with the gastric extracts tested, as well as the controls, are set in racks Into each of these tubes is measured by means of a graduated pipet, 2 cc of the glycyltryptophan-gastric extract mixture lying below the toluol in the recently incubated tubes To each tube are then added three drops of a 3 per cent glacial acetic acid in distilled water solution The tubes are well shaken Bromin vapor is allowed to flow into each tube until it appears amber yellow above the contained fluid The tubes are again shaken Examination by daylight (preferred) or by white artificial light is now made for evidences of the characteristic rose-pink reaction between the amino acid (tryptophan) and the bromin

**Tryptophan Test** As suggested by Weinstein, this is made as routine on the fresh gastric extracts inasmuch as, occasionally, swallowed saliva, amino acids, regurgitated duodenal contents and the like may give the bromin vapor reaction before incubation or without the addition of a dipeptid such as glycyltryptophan Five cc of each fresh filtered gastric extract are poured into test-tubes of 10 cc capacity acidulated with the 3 per cent acetic acid solution and treated with bromin vapor as above If no characteristic rose-pink color results the tubes are incubated with the corresponding specimens that have been mixed with glycyltryptophan solution For accurate work it has seemed best to us to cover these "tryptophan test" contents with a layer of toluol At the end of twelve twenty four and forty eight hours note is made of changes in color and these results are compared with those obtained with the preparations in the first series *Jour Am Med Assn* 1912 lxx 1008

patients In testing for tryptophan, before or after incubation, bromin vapor was preferred over bromin water It is more readily controlled quantitatively and permits of better color determination All end reactions were read by daylight

#### TYPICAL REACTIONS

When bromin vapor is used for the detection of amino-acid (tryptophan), its presence is indicated, even in small amounts, by lilac-violet to rose-pink shades The color is usually a lively one, and appears quickly Admixtures of much blood and bile produce, respectively, dirty, brownish-yellow and muddy-green to drab In such, gradations in shade are impossible High organic acidity often gives rich purple or magenta hues When the color change is opalescent, with bluish or delicate lilac cast, the results may be classed safely as negative

#### RESULTS

The gross results of our observations are as follows Of 1,175 gastric extracts from individuals with gastric symptoms, clinically 110, or 9.36 per cent, were glycytryptophan positive In the same cases, 24, or 2.04 per cent, were tryptophan positive, either before or after incubation Tables 1 and 2 show, respectively the number of positives with each test, associated with different diseases Tables 3 and 4 respectively consider the clinical and laboratory data

TABLE 1—SUMMARY OF CASES GIVING POSITIVE GLYCYLTRYPTOPHAN TEST

Diagnosis	No of Cases	Diagnosis	No of Cases
Carcinoma ventriculi	31	Achylia gastrica	6
Ulcus ventriculi	9	Appendicitis	8
Carcinoma of the liver	3	Primary anemia	3
Ulcer of duodenum	3	Syphilis—stomach	1
Non malignant pyloric obstruction	1	Various (gastritis, gastric neurosis	10
Cholecystitis	11	chronic diarrhea, epilepsy)	
Gall-stones	6		
Hypochlorhydria	7	Total	110
Achlorhydria	11		

TABLE 2—SUMMARY OF CASES GIVING POSITIVE TRYPTOPHAN TEST

Diagnosis	No of Cases	Diagnosis	No of Cases
Carcinoma ventriculi	7	Appendix lesions	1
Ulcus ventriculi	3	Various (neuroses, achlorhydria,	6
Ulcer duodenum	3	arteriosclerosis)	
Carcinoma of the liver	1		
Gall stones	3	Total	24

It will be noted that one of the valuable features of the tables is the fact that the majority of the cases exhibiting positive reactions were treated surgically, hence, the conclusions derived from consideration of the figures returned have a fairly definite pathologic basis

TABLE 3 —CLINICAL AND LABORATORY DATA OF THE CASES RETURNING POSITIVE GLYCYLTRYPTOPHAN TEST

Number and Name	Diagnosis	Total Acidity	Free HCl	Blood	Bile	Lactic Acid	Degree of Reaction
61563—Leslie	Gall bladder infect	46	36	+	0	0	+
9532—Graham	Anemia (post mort)	0	0	+	0	0	+
61743—Belanger	Duodenal ulcer—op	86	80	0	++	0	+
61000—Smith	Gall bladder	46	40	0	0	0	+
61795—Hillis	Gastritis chr	14	6	+	0	0	+
61857—Kise	Carcinoma stom—op	0	0	+++	0	0	+++
61802—Fuller	Gastritis, chr append	4	0	+	+	?	+
38406—Pew	Gall bladder infect	6	0	0	0	0	+++
53228—Reede	Gastric neurosis	18	18	+	0	0	+++
61852—Koss	Carcinoma stomach	4	0	+	0	0	+++
61910—Graybill	Carcinoma stomach—op	0	0	+++	0	+++	+
61812—Letoman	Epilepsy	10	10	+	+	0	+++
61940—Beck	Gastritis—chr	24	24	0	0	0	+
61862—Huseby	Gastric neurosis	40	30	0	+++	0	+
61974—Longtime	Gastritis—alcoholic	0	0	+	+	+	+++
62100—Schaffer	Carcinoma stomach—op	20	0	+	0	+	+
62171—Plan	Carcinoma stom opr	48	0	+	0	+++	+
62086—Haley	Gastritis—chr.	10	0	0	++	0	+
62089—Moldenhauer	Gastric ulcer	40	40	0	+	0	+
62219—Biehl	Carcinoma stom—op	24	12	+	0	0	+
62154—Ahlborn	Carcinoma stom opr	8	0	0	+	0	+++
62233—Flick	Carcinoma liver—expl	24	24	+	+	0	+++
62260—Chapman	Pyloric obstr non-malignant	40	32	+++	+	0	+
62399—Baum	Carcinoma stom—opr	0	0	+	0	0	+
53032—Kopplow	Duodenal ulcer—opr	50	50	Tr	+	0	+
62562—Dunn	Carcino Gall Bl opr	6	0	+	+	0	+
62665—Warner	Gastric ulcer	28	28	Tr	+	0	+++
37124—Nelson	Carcin stom recur	8	0	0	+	0	+
61072—Zielsdorf	Gall stones—opr	56	40	0	Tr	0	+
62876—Johnson	Cholecystitis	10	0	Tr	++	0	+++
62912—Erickson	Chr Ap op	22	18	Tr	+	0	+
62971—Maxwell	Chr Ap opr	22	0	0	+	0	+
62977—Hanson	Ulcer stomach	48	40	0	0	0	+
63026—Brooks	Chr Appendicitis	32	32	+	+	0	+
63051—Marian	Neg Stom Ap	36	32	0	+	0	+
63093—Taylor	Chr Diarrh stom neg	4	0	0	0	0	+
63129—Erickson	Stom ulcer and G B op	32	30	+	0	0	0
63130—Weech	Chr App opr	0	0	0	0	0	+
62699—Wright	Cholangitis	0	0	Tr	0	0	+
63030—Gladens	Carcinoma stomach	8	0	0	0	0	+
63241—Berend	Carcinoma stomach opr	56	18	+	0	0	+
63292—Glaesner	Gastric ulcer	46	46	+	+	0	+
63197—Smith	Multiple sclerosis	20	6	0	+	0	+
63335—Given	Duod ulcer, cholecystitis	48	40	0	+	0	+
52034—Rice	Recurrent Ca stomach	10	0	+	+	0	+
62876—Johnston	Syph stom	0	0	0	0	0	+
63506—Brägen	Gastritis	38	22	0	+	0	+
63547—Hanson	Resect stom c	0	0	+	0	0	+
63562—Arms	Arteriosclerosis	0	0	0	0	0	+
63600—Lutke	Appendicitis—neg	44	40	0	+	0	+
63616—Rarity	Appendix and G B op	12	0	0	+	0	+
63653—Allen	Ulcer stom opr	32	28	Tr	+	0	+
63636—Carlson	Gall stones—opr	22	0	0	0	0	+
63778—Thompson	Carc stom	14	0	+	+	+	+
36634—McEvan	Ulcer stom	40	30	+	0	0	+

TABLE 3—CLINICAL AND LABORATORY DATA OF THE CASES RETURNING POSITIVE  
GLYCOTRYPTOPHAN TEST (*Continued*)

Number and Name	Diagnosis	Total Acidity	Free HCl	Blood	Bile	Lactic Acid	Degree of Reaction*
63883—Bond	Gall stones—opr	6	6	0	0	0	+
64057—Atol	Hypochlorhydria	8	0	+	++	0	+
64039—Olson	Achlorhydria	0	0	0	0	0	+
61915—Even	Hypochlorhydria	4	4	0	0	0	+
64270—Gregg	Ulcer stom opr	50	46	+	0	0	+
64330—Schuler	Carc stomach	14	0	+	0	+	+
64360—Berg	Neurosis	54	50	0	+	0	+
64482—Sneath	Carc stom resect	8	0	+	0	0	+
64455—Norres	Hypochlorhydria	4	0	+	0	0	+
64281—Seedhug	Achylia gastr	0	0	+	0	0	+
34078—Johnston	Neuroses	42	40	0	0	0	+
64877—Hutchinson	Cholecystitis	1	0	0	0	0	+
65179—Otter	Appendicitis	36	26	0	Tr	0	+
65229—Arnold	Ca stom and liver	0	0	+	0	0	+
65293—Aklund	Achlorhydria	8	0	0	+	0	+
65337—Verner	Cholecystitis, appendix	16	0	0	Tr	0	+
37889—Gehrke	Appendicitis opr	12	12	Tr	0	0	+
65693—Rule	Gall stones and appendix opr	38	14	24	+	0	+
22528—Shaffer	Duod ulc opr	8	0	0	0	0	+
65703—Gaskill	Degen gast ulc	8	0	0	0	0	+
65835—Ellwell	Gen carc prim stom	0	0	0	0	0	+
65901—Hovelsrud	Carc stom	6	0	+	0	0	+
5231—Graff	Achlorhydria	8	0	0	+	0	+
65953—Eaton	Achlorhydria	12	0	0	+	0	+
66017—Richie	Carc stom	30	0	+	0	0	+
66108—Graham	Gall stones opr	8	0	0	+	0	+
66225—Bryant	Pernicious anemia	40	0	+	0	0	+
64942—Hester	Second anemia	10	0	0	0	0	+
66314—Spellman	Cholecystitis	30	30	0	+	0	+
66333—Wickman	Gall stones opr	10	0	+	0	0	+
66409—Bronson	Achlorhydria	20	0	+	0	0	+
66462—Bram	Gastric ulcer	26	26	+	0	0	+
56586—Carr	Cancer stom recur	48	48	0	0	0	+
66466—Stevens	Achlorhydria	48	0	0	0	0	+
63547—Harrison	Cancer stom resect	12	0	Tr	0	0	+
66511—Lane	Achlorhydria	4	0	0	0	0	+
66583—Miller	Cholecystitis	50	50	0	0	0	+
66644—Andrew	Carc stom	12	0	0	0	0	+
66787—Leutke	Achlorhydria	20	0	Tr	0	0	+
66904—Boe	Achlorhydria	34	0	Tr	0	0	+
66855—Fozenden	Carc stom opr	26	26	+	0	0	+
66864—Hennessy	Hypochlorhydria	12	12	+	0	0	+
67000—Stanley	Deg gast ulc	26	26	+	0	0	+
45833—Thompson	Hypochlorhydria	8	8	+	0	0	+
67110—McKay	Cancer stomach	20	0	+	0	+	+
67112—Rasmussen	Gastric neurosis	38	24	0	0	0	+
67077—Snyder	Carc liver and spleen	80	80	0	0	0	+
67206—Allen	Carc stom	14	0	0	+	0	+
67295—VanHook	Hypochlorhydria	18	8	Tr	+	0	+
67368—Tucker	Carc stom	50	50	+	0	0	+
67690—O'Rourke	Pernicious anemia	4	0	0	+	0	+
67928—Hayes	Ca stom P A (?)	14	0	+	0	0	+
67562—Wessling	Gall stone opr	12	0	0	0	0	+
67537—Owmen	Expl cancer stom	20	0	0	0	0	+
67644—Haggen	Achlorhydria	4	0	0	0	0	+

\*Degree of Reaction Lilac=+, Rose pink=++, Rose purple=+++

*Cancer* The total number of proven cases of cancer of the stomach, primary or secondary, in this series is eighty-seven. Of this number, thirty-one, or 35.6 per cent, gave positive glycytryptophan tests, while seven, or 8.04 per cent., were tryptophan positive. Of the thirty-one cases of cancer in which the glycytryptophan test was positive, the tryptophan test was positive but four times. In three cases in which the tryptophan test was positive, the glycytryptophan test was negative.

TABLE 4 —CLINICAL AND LABORATORY DATA OF THE CASES RETURNING POSITIVE TRYPTOPHAN TEST

Number and Name	Diagnosis	Total Acidity	Free HCl	Blood	Bile	Lactic Acid	Degree of Reaction*
61508—Theen	Stom neg	36	36	0	+	0	+
61496—Fitzsimmons	Duod ulcer opr	56	38	0	0	0	+
61567—Crane	Gastric ulcer	42	20	0	+	0	+
61552—Eldred	Carcinoma stom inop	38	18	+	0	+	++
62233—Flick	Carcinoma liver and G B	24	24	+	+	0	++
62784—Drechsler	Gastric ulcer clin	12	12	+	0	0	+
62876—Johnson	Achlorhydria and G B	10	0	+	+++	0	+
62865—Zenk	Appendix chronic	24	18	Tr	+	0	+
63051—Marion	Gastric neurosis	36	32	0	+	0	+
63230—Gladens	Carcinoma stom (mass)	8	0	0	0	0	+
63241—Buiend	Gastric carcinoma, resect	58	18	+	0	0	+
63221—Quinn	Gall-stone empyema G B	20	20	0	Tr	0	+
63414—Hanson	Duodenal ulcer opr	80	80	0	+	0	+
63408—Lynch	Carcinoma stom opr	66	60	0	0	0	+
63653—Allen	Gastric ulcer clin	32	28	Tr	0	0	+
63354—Kissman	Tabes—cruces	4	0	+	0	0	+
63563—Arms	Arteriosclerosis Gen	0	0	0	0	0	+
63536—Carlson	Gall stone opr	22	0	0	0	0	+
64394—Davis	Duodenal ulcer opr	66	60	0	0	0	+
64294—Thoet	Carcinoma stom opr	14	4	+	0	+	++
65693—Rule	Gall stones and append opr	38	14	+	0	0	++
5231—Graf	Gastric ulcer degen post opr	8	0	0	+	0	++
56586—Carr	Carcinoma stom recur	48	0	0	0	0	+
67112—Rasmussen	Gastric neurosis	38	24	0	+	0	++

\*Degree of Reaction Lilac=+, Rose-pink=++, Rose-purple=+++

Of nine gastric ulcers with fair evidence of carcinomatous degeneration (of the type described by MacCarty<sup>14</sup>), two, or 22.2 per cent, gave the glycytryptophan reaction. In these same cases there was no positive tryptophan test. If we combine the returns from these cases with those from the specimens of advanced carcinoma, we note that the glycytryptophan test is positive in 35.4 per cent and the tryptophan in 7.28 per cent, or the glycytryptophan test is positive approximately five times as frequently as is the tryptophan test.

<sup>14</sup> MacCarty Surg Gyn and Obst 1910 v 440



*Gastric Ulcer* In none of thirty-five operated gastric ulcers (microscopically carcinoma-free) was the glycytryptophan test positive. The tryptophan reaction was obtained once.

Thirty-nine cases were clinically diagnosed as gastric ulcer. Three of these (7.4 per cent) were glycytryptophan-positive, and two (5.2 per cent) were tryptophan-positive.

*Duodenal Ulcer* Operations were performed on seventy-eight patients with duodenal ulcers. Of this number, three (2.6 per cent) gave glycytryptophan and tryptophan tests. They were not identical cases and the reactions were not always associated with low acidity.

Fifty-seven individuals had duodenal ulcer, clinically. One (1.7 per cent) was glycytryptophan-positive. None gave the tryptophan test.

TABLE 5—THE RELATION OF GLYCYLTRYPTOPHAN TEST TO ACIDITY

Group	No of Positives	No of Negatives	Group	No of Positives	No of Negatives
Extracts having no acidity	14	20	Extracts having decreased T. A.	88	515
Extracts having no free HCl	52	31	Extracts having normal T. A.	17	213
Extracts having diminished HCl	15	214	Extracts having increased T. A.	5	337
Extracts having normal HCl	22	369	Totals	110	1,065
Extracts having increased HCl	7	431	Extracts having lactic acid	11	33
Totals	110	1,065			

*Other Gastric Conditions* It has been advanced by Weinstein, Warfield, and Sanford and Rosenbloom that positive glycytryptophan reactions are usually obtained in gastric extracts exhibiting achylia or low hydrochloric acid. These reactions are claimed to result from the presence of a peptid-splitting enzyme (Warfield) existing in saliva. Gies<sup>15</sup> thinks that mouth-bacteria may be capable of splitting simple peptides under these conditions. In order to determine the results in our cases from the view point of acidity, we have compiled Tables 5 and 6. It will be seen that about 60 per cent of the positive glycytryptophan tests were obtained from extracts showing no free hydrochloric acid, while in an additional 13.6 per cent, the free hydrochloric acid was low. In other words, nearly three-fourths of the positives occurred in gastric extracts showing diminished acidity. Table 5 also brings out the interesting fact that approximately 80 per cent of the

15 Gies. Quoted by Weinstein, Jour. Am. Med. Assn., 1911, LVII, 1420.

glycyltryptophan reactions were returned by contents in which the total acidity was low

The support which these figures apparently give to Warfield's saliva ferment-action on peptids is qualified when one considers the negative glycyltryptophan tests in Table 5. Fifty-one of these extracts showed no free hydrochloric acid. In 214 extracts the free hydrochloric content was diminished. The combination of these results demonstrates that about one-fourth (24.8 per cent) of the negatives was associated with low free hydrochloric acid. It could scarcely be maintained that all these extracts were saliva-free. Table 3 shows that some of the extracts were from cancerous patients. Approximately one-half (48.3 per cent) of the negative glycyltryptophan tests were on extracts with diminished total acidity.

TABLE 6—THE RELATION OF TRYPTOPHAN TEST TO ACIDITY

Group	No of Positives	No of Negatives	Group	No of Positives	No of Negatives
Extracts having no acidity .	1	33	Extracts having decreased T A	17	586
Extracts having no free HCl	6	77	Extracts having normal T A	2	228
Extracts having diminished HCl	10	219	Extracts having increased T A	5	337
Extracts having normal HCl	4	387	Totals	24	1,151
Extracts having increased HCl	3	435	Extracts having lactic acid	2	42
Totals	24	1,151			

A consideration of the relation of the tryptophan test to acidity is of interest. Of the positives seven, or 28.9 per cent, of the contents contained no free hydrochloric acid. In seventeen (75 per cent) of the positives the free hydrochloric acid was diminished or absent. This combined figure is practically identical with that returned by the glycyltryptophan positives, although the percentage of extracts containing no free acid is much lower. In the tryptophan positives it will be seen that 75 per cent showed diminished total acidity as against 80 per cent in the case of glycyltryptophan positives.

Studying the negative tryptophan reactions, we note that in 329 instances (28.6 per cent) there was absent or diminished free acid, while in 586 cases (50.8 per cent) the total acidity was low. These figures closely approximate those shown by the tabulations from the negative glycyltryptophan reactions.

It would appear that Weinstein's contention that his tryptophan test removes the consideration of contaminating saliva as a source of

error is not borne out by our study. Further, the presence of negative glycytryptophan reaction, in so large a percentage of extracts with low acidity, leads one to the opinion that the significance of the peptidase, said to exist in saliva, as a factor in hydrolyzing glycytryptophan added to gastric extracts, is quite questionable. This opinion is substantiated by work we have done on saliva, soon to be reported.

*Organic Acid* Ten per cent of the positive glycytryptophan tests were associated with the presence of lactic acid. With the exception of one, the cases were carcinoma. Thirty-three negative reactions (3.9 per cent) were in contents containing lactic acid. Eight and one-third per cent of the positive tryptophan tests were present in lactic-acid-containing extracts while forty-two (3.6 per cent) negative tryptophan contents contained lactic acid. It would seem that organic acids have little bearing on the relative variation of the two tests.

TABLE 7

(A) THE RELATION OF BILE TO GLYCYL-TRYPTOPHAN TEST				(B) THE RELATION OF BILE TO TRYPTOPHAN TEST			
Groups		Bile present	Bile absent	Groups		Bile present	Bile absent
Glycytryptophan positive		39	71	Tryptophan positive		10	14
Glycytryptophan negative		320	945	Tryptophan negative		349	802
Totals		359	816	Totals		359	816

Of the entire number of gastric extracts (1,175) analyzed in this series, forty-four, or 3.7 per cent, contained lactic acid by the controlled Uffelmann test. Of the cases proved to be carcinoma ventriculi, lactic acid was present in twenty-five (28.7 per cent). As we have shown in these cases, the glycytryptophan reaction was positive in thirty-one (35.6 per cent) and the tryptophan test in seven (8.04 per cent). The relatively low percentage of extracts containing lactic acid may be explained on the basis of early diagnosis, many cases being operated on before marked obstruction and retention had developed. Emerson<sup>10</sup> states that in his series of cases of carcinoma ventriculi, lactic acid was present in approximately 90 per cent. From our experience, it would appear that the great majority of his cases were far advanced and exhibited marked retention. High mixed organic acidity frequently gives confusing Uffelmann reactions.

It has been held that the *chyle* in gastric extracts vitiates the glycytryptophan test, but need not be considered when making the tryptophan test. The presence of bile or evidences of tryptic digestion has been used as proof that duodenal contents have been mixed with gastric juice.

16 Emerson "Clinical Diagnosis," 1906

The significance of this supposition is shown by analysis of Table 7. The gastric extracts were judged macroscopically as to the presence of bile and were also tested by means of the Pettinkofer or the fuming nitric acid reaction. It will be seen (a) that of 110 positive glycytryptophan reactions, thirty-nine (35.4 per cent) contained bile, of 1,065 negative reactions, 320 (30.0 per cent) showed bile, of the twenty-four positive tryptophan tests (b), ten (41.6 per cent) were in bile-containing extracts, while 349 (30.4 per cent) negative tryptophan tests were bile-positive. These figures do not demonstrate that the tryptophan test is uninfluenced by bile in the extracts. It is worthy of note that a relatively high number of both glycytryptophan and tryptophan reactions are found in bile-containing chyme.

TABLE 8

(A) THE RELATION OF BLOOD TO GLYCYTRYPTOPHAN TEST

Groups	Bile present	Bile absent
Glycytryptophan positive	56	54
Glycytryptophan negative	236	829
Totals	292	883

(B) THE RELATION OF BLOOD TO TRYPTOPHAN TEST

Groups	Bile present	Bile absent
Tryptophan positive	10	14
Tryptophan negative	282	869
Totals	292	883

*The effect of blood*, traumatic or "occult," in gastric extracts has at least two points worthy of consideration with regard to the glycytryptophan and tryptophan tests. Traumatic blood of itself gives a tan or definitely red cast to filtrates. A color reaction such as we are discussing is readily effected by such shades. The second point of note is the possibility of tryptophan resulting from split digestion products of the blood itself, particularly in those cases in which there is marked gastric retention with much flora. Table 8 furnishes interesting data on the above points. In fifty-six (50.9 per cent) of the glycytryptophan positive extracts, blood, traumatic or altered, (benzidin test) was present. Of the glycytryptophan negative extracts, in 236 (22 per cent) blood was demonstrated. Of the tryptophan positive extracts, ten (41.6 per cent) contained blood. In 282 (24.6 per cent) tryptophan negatives, blood was proved. These figures for both tests so closely approximate that it does not seem possible to state that advantage lies with either. The relatively high percentage of positives in extracts containing blood should, however, be borne in mind.

## SUMMARY

The work submitted makes apparent the following:

1. In our series more than one-third of the proved cases of cancer of the stomach gave positive glycytryptophan reactions, more than one-fourth were lactic-acid-positive and about one-thirteenth of the number

exhibited the tryptophan test. Diagnosis of malignant disease of the stomach was in each case quite possible, independent of the above chemical reactions. As a test associated with cancer of the stomach, it will be seen that in our series the glycytryptophan reaction proved more consistent than tests for common organic or existing free amino-acid (tryptophan).

2 While gastric conditions other than cancer exhibit positive glycytryptophan reactions, in no single class of disease of the stomach is this test obtained so frequently as in cancer. This fact is of considerable significance chemically and, perhaps, etiologically. While cancer of the stomach can doubtless be diagnosticated clinically without the glycytryptophan test, one cannot state that the study of this and allied reactions will prove valueless.

3 Our work does not show that the tryptophan test is, as has been advanced, pathognomonic of cancer.

4 Low free hydrochloric or total acidity is frequently determined in gastric contents exhibiting positive glycytryptophan, lactic acid and tryptophan reactions. One cannot state positively that this diminished acidity is causative. Many cases of low acidity were negative to the above tests.

5 Approximately one-half of the positive glycytryptophan and tryptophan reactions were in gastric extracts containing bile and blood elements. Approximately one-fourth of the negative extracts contained blood and bile elements.

# AN EXPERIMENTAL STUDY OF RACIAL DEGENERATION IN MAMMALS TREATED WITH ALCOHOL

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It is recognized, by most observers who have studied the subject, that alcohol may play an important rôle in the causation of monstrosities and of structural defects predisposing to later disease. This view is based largely on observations on defective human beings, and the probability of its truth is sufficiently established to warrant further careful experimental analysis.

The quality of an offspring depends on two factors, the perfection of the germ cells from which it arises and the nature of the environment in which it develops. Diseased and weakened germ-cells give rise to a defective individual under all circumstances, while perfect germ-cells produce a perfect offspring *only* when the embryo develops in a normal or favorable environment. These facts may be readily demonstrated in lower vertebrates in which the development of the egg is outside the mother's body. The egg or spermatozoon in such cases may easily be chemically modified or injured before fertilization, and the embryo itself may be affected in various ways during its development by subjecting it to unusual surroundings, either physical or chemical. In other animals, such as mammals, in which the embryo develops internally, the proposition likewise holds true. In these animals, however, the problem is more difficult to completely analyze. The reactions of the parental body, the secondary conditions induced by the experimental treatment and other sources of error should be fully considered in determining whether an effect shown by the offspring is directly due to the applied stimulus or to secondary conditions. In the lower vertebrates it has been shown that given doses of certain substances induce definite developmental defects. The defects are directly due to the treatment. Is it possible by the addition of certain chemicals to the mammalian body to obtain similar definite changes in either the germ-cells or the developing embryo?

In the present paper I shall endeavor to show that alcohol does act directly on the germ-cells of mammals to a sufficient degree to render them incapable of producing normal offspring and further, that similar treatment administered to the pregnant female may likewise act directly on the developing embryo so as to modify its resulting structure.

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\*From the Anatomical Laboratory, Cornell University Medical College.

\*Manuscript submitted for publication May 19, 1912.

First to appreciate fully the general status of the problem it is well to consider in a somewhat critical manner the literature pertaining to the actions of alcohol and other substances on the reproductive glands and developing embryos of man and lower animals

#### DISCUSSION OF LITERATURE

There is an abundant literature relating to the effects of alcohol on the offspring, though little of it is scientifically reliable. I have attempted to select those cases which seem most trustworthy. Since we are more interested in the general problem of the effects of parental poisoning on the germ-cells and the embryo in mammals I have also collected the works relating to injurious substances other than alcohol. The observations and statistics on human beings in various countries are reliable only in so far as they may be substantiated and borne out by controlled experiments on lower animals. Yet in the light of animal experiments many of these human records become of surprising interest, although few if any of them may be accepted entirely as they stand.<sup>1</sup>

#### EFFECT ON THE MALE GERM-CELLS

It is a well known and universally accepted fact that alcohol does cause changes and degeneration in many of the body tissues of man. The question naturally presents itself, How, then, can the reproductive tissues escape? Nicloux and Renault have shown that alcohol has a decided affinity for the reproductive glands. In the testicular tissues and the seminal fluid an amount of alcohol is soon present which almost equals that in the blood of a person having recently taken alcohol. The proportion of alcohol in the testis as compared with that in the blood was as 2 to 3, and in the ovary of female mammals as 3 to 5. The genital glands show as great an affinity for this substance as does the nervous system. From these observations it must necessarily follow that alcohol may act on the ripe spermatozoon shortly before the time when it fertilizes the egg, and since an affected spermatozoon gives rise to a defective individual we have a probable explanation for many of the recorded defects attributed to drunkenness at the time of conception. A male, even for the first time in a state of acute intoxication, is probably more apt to beget an abnormal offspring by fertilizing an egg at this particular period than is a non-intoxicated male although a frequent user of alcohol. The experimental data on the sensitiveness of the spermatozoon and the observations on the presence of alcohol in the seminal fluid warrant this statement

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1 Most of the literature is devoted to considerations of disease and insanity statistics and the family records of degenerates. The data are often collected in a careless fashion so that the *actual observations* are not always scientifically correct though the records are carefully and fully computed.

Lappich claims to have observed ninety-seven children resulting from such conceptions. Only fourteen of these were without noticeable defects. Eighty-three of them showed various abnormal conditions, twenty-eight were scrofulous,<sup>2</sup> three had "weak lungs," three showed different atrophic conditions, one watery brain, four were feeble-minded, etc. Others have made similar observations. Sullivan reported seven cases of drunkenness during conception which are fairly authentic. Six of the offspring died in convulsions after a few months, and the seventh was still-born.

Thus one finds proof by Nicloux and Renault that alcohol does reach the reproductive glands and, therefore, may affect the egg or sperm-cell, and observations seem to indicate that this effect expresses itself in the condition of the resulting offspring. Experiments on lower animals support the probability. When the perfectly normal spermatozoa of frogs are treated with  $\gamma$ -ray or radium, Bardeen and O. Hertwig have shown that normal eggs fertilized by such spermatozoa all develop abnormally. Todde found that the offspring from alcoholized roosters were not quite normal and that the roosters did not succeed as well as normally in fertilizing eggs.

Combemale, 1888, was the first to experiment on the influence of alcohol on the mammalian offspring. He treated a dog for eight months with absinthe (11 gr per day per kilo of animal weight) and paired this alcoholized dog with a normal bitch. Twelve young resulted, two were born dead, three died within fourteen days and the others died between thirty-two and sixty-seven days of intestinal catarrh, tuberculosis, etc. In a second experiment both parents were mated while normal, then the female was made drunk for twenty-three days (2.75 to 5 gr absinthe of 72 per cent per day per kilo). Of six young three were still-born, two had normal bodies though of weak intelligence, while one moved slowly and was very stupid. The last individual, a female, was later paired with a normal intelligent non-alcoholic dog. She gave only three young, one was deformed club-footed with abnormal teeth, the second had a patent ductus arteriosus and died after fourteen days, while the third was poorly muscled in the hinder parts and died a few hours after birth. Thus the effects in the second generation are as pronounced as in the first although neither parent had themselves received any alcohol. The only criticism against Combemale's experiments is that an insufficient number of animals was used. Dogs often give defective pups and these may have been from poor stock, though such an interpretation is really not probable and his results are supported by subsequent workers.

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<sup>2</sup> Imbault P. Contribution à l'étude de la fréquence de la tuberculose chez les alcooliques. Thèse de Paris 1901. Imbault found that tuberculosis was about as common among the children of alcoholic parentage as among those of tuberculous parents.



Hodge, in 1897, obtained similar results. From one pair of alcoholic dogs he obtained twenty-three pups, eight were deformed and nine were born dead, while only four lived. In a control set forty-one individuals lived, four were deformed and there were no still-births.

Laitinen treated rabbits and guinea-pigs with various doses of alcohol and studied chiefly the changes in body conditions as to resistance against disease toxins, etc. He has also recorded observations on the offspring produced by these animals during the experiment. He is apparently more interested in the problem of the misuse of alcohol than in the scientific study of the influence of injurious substances on the offspring and in his enthusiasm to prove the point with extremely small doses of alcohol he fails to fully consider both sides of his own tables.

He used daily doses of alcohol as small as 0.1 cc per kilo of animal weight. This would amount to a small glass (200 cc) of beer per day for an adult man. His tables on careful study fail to show that so little alcohol actually does injure the offspring of the treated animals.

With alcoholized rabbits Laitinen finds that only 38.71 per cent of the young live, while 61.29 per cent are still-born or die shortly after birth. In the control, however, only 45.83 per cent lived, while 54.17 per cent, more than half, were still-born or died shortly after birth. The animals were kept all together in a general cage and the pregnant females were only separated shortly before the young reached term. This is scarcely an approved method in breeding experiments, and the fact that young rabbits are so delicate and are born in a rather poorly developed state makes their careful handling necessary. The fact that more than half of the control young die, 54.17 per cent, would indicate the danger of drawing conclusions from a death-rate only 7 per cent higher among the offspring of the treated animals.

The case of the guinea-pigs is also indifferent, 78.26 per cent of the control young lived, while 21.75 per cent, or a little more than one-fifth, of them died. The large majority of the young of treated parents also lived, 63.24 per cent, while 37.76 per cent died. In both sets more of the young lived than died. Guinea-pigs are easily reared and are born in a well-developed condition. On the other hand, in both of the rabbit sets more of the young died than lived.

Results which I shall record below show that larger doses of alcohol do produce definite effects on the offspring. My experiments have been performed in a different manner and from another point of view. The primary object has been to regulate or control the type of development in mammals in a definite fashion as I had succeeded in doing with lower vertebrates. In these experiments it will be demonstrated that an alcoholized male guinea-pig almost invariably begets a defective offspring even when bred to a vigorous normal female.

Rosch was the first to study the reproductive glands of alcoholics, in 1837, and found degeneration of the testicles. Lancereaux described a parenchymatous degeneration of the seminal canals. Simmonds (1898) found azoospermia in 60 per cent of cases of chronic alcoholism, 5 per cent of these men were sterile. Kyrle reported three cases of total atrophy of the testicular parenchyma in which death had resulted from cirrhosis of the liver due to alcohol. Kyrle attributed the atrophy of the testicle to the cirrhosis of the liver and not to chronic alcoholism.

Bertholet (1909) made an extensive examination of the influence of alcohol on the histological structure of the germ glands, more particularly on the testicles of chronic alcoholics. He found testicular atrophy in alcoholics with no cirrhosis of the liver. Bertholet observed partial atrophy of the testicles in the majority of seventy-five chronic alcoholics. These men died between the ages of 24 and 57 years, the greatest mortality being between 30 and 50 years. In thirty-seven cases, excluding syphilitics, a microscopical examination showed a more or less diffuse atrophy of the testicular parenchyma and a sclerosis of the interstitial connective tissue. The testicles were small and hard. The canals were greatly reduced in size and their lumina obliterated. Spermatogonia were atrophic. It was generally impossible to differentiate spermatocytes or spermatids. There were no dividing cells and no spermatozoa. The thick basal membrane of the canals was formed of connective tissue lamellæ with concentrated spindle cells. These conditions with slight variations were found in twenty-four cases. Such atrophic structures were already present in a drinker only 29 years old. In four cases of cirrhosis of the liver the testicular atrophy had not progressed very far and spermatozoa were still present. In five cases the microscopical conditions were less marked.

While these appearances of the basal membrane may also be observed in non-alcoholics, the extreme conditions of atrophy of the testicles were only found in alcoholics. Observing the testicles of non-alcoholics that had died of various chronic illnesses such as tuberculosis, no atrophy of the testicles or thickening of the membrana propria was found. Two such old men of 70 and 91 years still possessed spermatozoa in the canals. Bertholet concludes that the atrophy he has observed cannot be due to old age, but is due to the hurtful effects of chronic alcoholism on the reproductive glands.

Bertholet has also reported an atrophy of the ovary and ova in female alcoholics. Weichselbaum has confirmed the observations of Bertholet at his institute in Vienna.

Bertholet's observations are most important and his drawings bear out his statements. On the other hand it is certain that the chronic alcoholic is not so often rendered sterile as his study might lead one to

believe Judging from the statistics it is not rare to find alcoholics with large families My experiments on animals may not be of sufficient duration at the present time, yet I have male guinea-pigs that have been almost intoxicated on alcohol once per day for six days a week extending over a period of nineteen months These animals are still splendid breeders Nineteen months of a guinea-pig's existence is proportionally equal to a good fraction of a human life Many of these animals have been killed and then testicles examined microscopically and found to be normal In some cases where a male had failed to succeed in impregnating the female for several times, he was partially castrated, one testicle being taken out In this case the testicle was found to be normal and the same male has since given offspring by other females Ovaries have been examined in a similar way, and in no individual has the alcohol treatment caused a visible structural change in the reproductive glands The actual physiological proof of the efficiency of the organs is shown by the ability of all animals to reproduce The important point which I shall show in the following pages is that although there is no visible structural change in the germ-cells nevertheless, they have been modified chemically to an extent sufficient to cause them to give rise to defective embryos or weakened individuals which die shortly after birth

Schweighofer has recorded an interesting individual case A normal woman married a normal man and had three sound children The husband died and she married a drunkard and gave birth to three other children, one of these became a drunkard, one had infantilism, while the third was a social degenerate and drunkard The first two of these children contracted tuberculosis, which had never before been in the family The woman married a third time and by this sober husband she again produced sound children This is an important human experiment The female was first tested with a normal male and gave normal offspring, when mated with an alcoholic male the progeny were defective as a result of his poisoned condition She was again tested with a normal male and found to be still capable of giving sound offspring A number of such cases are on record

Schweighofer states from a mass of observations that the offspring of drunkards, themselves of good sound families, show much degeneracy and defective conditions

Other substances than alcohol seem to act directly on the germ-cells of mammals Constantine Paul long ago pointed out that the children of people working in lead were often defective He made the interesting observation that when the father alone was employed in such work his children were affected by it

All of the above experiments and observations refer more particularly to the action of injurious substances on the germ-cells of the male parent

This is the crucial proof of an effect on the germ cells. The case of the female is complex, since the substance may produce a germinal defect by acting on the egg, or it may also directly affect the developing embryo and thus act as an environmental influence on development.

#### THE FEMALE GERM-CELLS AND THE DEVELOPING EMBRYO

Herbst's classical lithium experiments show the influence of salt solutions on developing eggs. The experiments of J. Loeb on fish embryos, those of Morgan on the frog and my experiments on fish all show the marked influence of inorganic salts and organic compounds on the development of the embryo. I showed that alcohol caused all known

TABLE 1—EFFECTS OF WORKING IN LEAD

	No of Cases	No of Pregnancies	Abortions, Pre-mature Labor, Still-Births	Living Births	Remarks
Females showing lead poisoning symptoms	4	15	13	2	One of the living children died in 24 hours
Females working in type foundry, previously had normal pregnancies	5	36	29	7	Four died in first year
Female in type foundry, five pregnancies	1	5	5	0	
Females working intermittently, while there	3	3	3	0	After being away for some time had healthy children
Females with blue line on gums, only sign of poisoning	6	29	21	8	
Male alone exposed	7	32	12	20	8 died first year, 4 second year, 5 third year
Total		120	83	37	22 died under three years

gross abnormalities of the brain in fish embryos and also gave all possible abnormal conditions of the eyes. Other substances such as ether, chloroform, chlorbutanol (chloretone), etc., also had a peculiar affinity for the developing central nervous system. These substances also act physiologically on the central nervous system of the adult.

Constantine Paul not only showed the injurious effects of lead on the paternal germ-cells but also recorded instructive data regarding the offspring of women working in lead. More recent observers have pointed out the frequency of idiocy and other defects among the children of lead workers. Adam has tabulated the findings of Constantine Paul as shown in Table 1.

Forel states that acute alcoholic intoxication affects not only the brain, but as Nieloux has shown, the alcohol passes quickly to the cells of the testicle or ovary and Bertholet's observations confirm this. A conception which takes place while the cells are in this poisoned state often results in a feeble-minded or degenerate child. The facts furnished by experiments on the eggs and spermatozoa of lower animals lend the strongest support to this idea and there is no experimental evidence that can be interpreted as opposed to Forel's statement.

Chronic alcoholics who consume daily certain amounts of alcohol slowly injure their germ cells. By intensive use of alcohol these cells may actually be killed or caused to atrophy. This, however, is the extreme case and before reaching a state of atrophy the cells pass through various grades of defectiveness. The stages may show no anatomic changes, but their physiologic state is indicated by the defective individuals to which they give rise in development.

Bezzola found that in Switzerland, in the years 1880 to 1890, there were 8 190 idiots. Most of the idiots were born in wine districts, and the season for the maximum birth of such children was nine months after the great national feasts, indicating, possibly, that idiots were conceived during the period of heaviest drinking. Schweighofer found the same relationship between the season for the greatest number of still-births and the feast seasons in Austria.

Martin studied the family histories of eighty-three epileptic girls in the Salpêtrière (Paris). Sixty had alcoholic parents, while of the other twenty-three alcoholism was doubtful or absent in their parents. The sixty girls from alcoholic parentage had 244 sisters, of them 132, or 54.1 per cent, were dead, forty-eight, or 19.7 per cent, had had spasms during childhood.

Studying the direct ancestry of 370 insane people, Jenny Koller (in 1895) found that there were twice as many drinkers as were found in the direct ancestry of 370 sound people selected at random. Others have recorded similar observations.

Karl Pearson and Miss Elderson studied statistically 3,000 school children in England. They concluded that the children of alcoholics were often heavier than those of sober parents, they were also less diseased, had little epilepsy and tuberculosis and are actually cleverer in school. They found, however, a greater mortality among the children of alcoholics, especially of female drinkers, and concluded that only the stronger children lived, and therefore, their quality was good.

These studies have been widely criticised, and are probably not based on very thorough biological observations. They consider, in the first place, only school children. It is not known whether the parents were drunkards at the time of, or previous to the conception. The degenerate

offspring of alcoholics could not enter school. The results would doubtless have been quite different if the inmates of an institution for defective children had been studied. The great body of evidence from anatomic studies of the reproductive glands of alcoholics, the animal experiments and disease records are all opposed to Pearson's conclusions.

The most valuable study that I have been able to find on the influence of alcohol on the human offspring is that of Sullivan in 1899.

Sullivan emphasizes the point that while much effort has been made to record alcoholism in the ancestry of degenerates, the important study must be made on degeneracy in the descendants of well-observed alcoholics. He studied the alcoholics among the female population of the Liverpool prison and as far as possible chose cases of alcoholism that were unaccompanied by disease or other degenerate factors.

Localization of alcoholic lesions in the body are not well worked out, yet it is unquestionable that in the criminal, as in insane alcoholics, the nervous manifestations of the intoxication occur with notable frequency, while non-nervous disorders are rare or secondary. Of these alcoholic females, thirty-one had had one or more attacks of alcoholic delirium, twenty-four had occasional hallucinations, suicidal impulses, disorders of cutaneous sensibility, and clasp in the extremities was noted in a considerable number of cases. In these patients tissues other than the nervous, so far as examination of the patients themselves could show, were comparatively immune to the poison of alcohol, and this was also true of their alcoholic relatives.

There were 100 women in the series Sullivan observed, and twenty of these gave details of female relatives of drunken habits who had children. To these 120 females were born 600 children, of whom 265, or 44.2 per cent, lived over two years, 335, or 55.8 per cent, died under 2 years or were still-born. Twenty-one of the women observed gave records of sober relatives, sisters or daughters married to sober men. The twenty-one drunken females had 125 children, sixty-nine or 55.2 per cent, died under 2 years, the twenty-eight sober females had 138 children, and thirty-three, or 23.9 per cent, of them died under 2 years. The death-rate of children from the drunken mothers was nearly two and one-half times greater than that of the children of their near-blood relatives who were non-alcoholic. The alcoholics however are poor mothers and take little care of their children. This fact might possibly account for the entire difference though such a deduction is extremely improbable.

The progressive births in the alcoholic family show interesting records. In eighty cases the number of children reached or exceeded 10.

The tabulation shows an increasingly poor condition. The records of two individual cases may be mentioned by way of illustration.

Case 5 Three first children healthy, fourth of weak intelligence, fifth epileptic idiot sixth still born, and finally, an abortion

Case 10 First child survived to adult life, second died of infection as child, two infants then died in convulsions in first few months, then a still birth

These records stand in interesting contrast with those known for syphilitic mothers in which each conception seems to be more and more nearly successful until a weak offspring is born, and finally such a mother may give birth to an apparently normal child. The syphilitic is gradually becoming less diseased and is overcoming the toxic condition as time goes on, while these alcoholic women are on the contrary becoming more and more saturated with the poison, and for this reason each succeeding birth is more decidedly defective.

TABLE 2—SHOWING PERCENTAGE OF STILL BORN AND CHILDREN WHO DIED IN AN ALCOHOLIC FAMILY

	Cases	Died or Still Born, Per cent	Still Born, Per cent
First born	80	33.7	6.2
Second born	80	50.0	11.2
Third born	80	52.6	7.6
Fourth and fifth born	111	65.7	10.8
Sixth to tenth born	93	72.0	17.2

The records were worse for women who had begun drinking some time previous to the first conception. In thirty-one cases they had been drinking for at least two years before the first pregnancy. Of 118 children born to these, seventy-four were still-born or died in infancy, giving 62.7 per cent as compared with a death-rate of 54.1 per cent for the others of the series.

In only thirty-nine of the cases were the women's parents sober people, yet the records of the offspring from these women were equally as bad as those from the sixty-one mothers who had alcoholic parents. This is a significant fact, since it indicates most strongly that the defective children are due to the direct effect of alcoholism and not to other degenerate conditions. Sullivan recorded seven known cases of conception during a state of drunkenness, six of the children died in convulsions in a few months, while the seventh was still-born.

Another observation by Sullivan which indicates that the alcohol as such is the cause of defectiveness was the fact that mothers imprisoned during pregnancy gave birth to a better child since the drinking was stopped.

Sixty per cent of the children of all these mothers died in convulsions. This is a common manner of death for the offspring from the alcoholic mammals I have studied.

Kende found that of twenty-one families in which the father and mother both drank, ten were childless, while of the twenty-four children in the other eleven families, sixteen died early and only three were entirely normal. In eighteen families in which only the father drank, but three children in twenty-one were entirely sound, while there were many abortions and several cases of sterility.

There are numerous statistical facts showing a large percentage of alcoholics in the ancestry of prostitutes, degenerates and other inferior classes. All of the studies seem to show that alcoholism and the degenerate condition tend to occur in the same family, and Sullivan seems to control the case by showing that in some instances, at least, alcohol is the cause of degeneracy.

The real, crucial proof of the direct action of alcohol must come, however, from experiments on lower animals, where the sources of error may be entirely controlled.

Adam states "The general belief (and we regard it as well founded) is that the children of the sot are as a body of lowered intelligence and vitality with unstable self-control." He recognizes the great difficulty of statistically proving this in man, since alcoholism is so often the accompaniment of weakness and hereditary taint, and may not be the primary cause of the condition in many families. With animals, however, the experimenter is enabled to prove that alcohol does induce a primarily degenerate condition.

One could continue to enumerate records showing the effect of alcoholism on the human offspring, yet a sufficient number of studies have been considered to show how strongly indicative the evidence is that alcohol is really the direct cause of defects in many cases. There is also little doubt that alcoholism is sometimes acquired by perfectly normal human beings, and when the tissues of such people become affected by alcohol they no doubt give rise to defective and abnormal offspring.

It is, however, an undeniable fact that alcoholism in man is very frequently an accompaniment of various degenerate conditions and these conditions are oftentimes within themselves sufficient to account for further degeneration in the offspring. We shall, therefore, consider more fully at this point the evidence furnished by animal experimentation.

#### ANIMAL EXPERIMENTS

As stated above the problem is broader than the subject of alcoholism. If it is shown that any toxic substance can act on the germ cell or developing embryo in such a manner as to change or destroy it



development, it necessarily follows that alcohol may induce a more or less equivalent condition, since it is definitely known to act on all animal tissues. I shall, therefore, mention the experiments with alcohol in particular, and at the same time consider other of the striking examples of environmental effects on the developing eggs of lower animals.

H. E. Ziegler treated sea-urchin's eggs with ethyl-alcohol. A 1 per cent solution in sea-water delayed development, a 2 per cent solution also delayed development and caused abnormal embryos, while a 4 per cent solution prevented all development. The peculiarly typical larvæ of the sea-urchin which Herbst induced by the addition of lithium salts to sea-water have been mentioned above. Herbst's experiments furnish a striking example of a characteristic response on the part of the developing organism to a definite chemical treatment. Morgan obtained similarly definite results by treating frog's eggs with lithium, and I have shown a somewhat comparable response for the fish's egg. Other salts may give the same types of larvæ, as occurred in these cases, as McClendon has shown for the fish, and as I previously pointed out in several of my studies on the cyclopean defect. Yet with certain doses of given substances one gets greater numbers of the same defect than with any other treatment. It is not surprising that a few individuals of any one deformed type may occur in a number of different solutions. The important fact is, that with a particular treatment one is able to obtain on all occasions a large number of embryos exhibiting a perfectly clear-cut, definite defect.

Ridge got decided results by treating the eggs of the blue bottle-fly and frogs with alcohol. In solutions of 1/100 per cent alcohol in water the development was slow. In 1/20 per cent solutions development proceeded for only a short time and the eggs died. In one per cent alcohol only one or two eggs started.

Ovize made an interesting observation on the influence of alcoholic fumes on developing hen's eggs. An incubator containing 160 eggs was in a cellar in which wine and brandy were being distilled. Seventy-eight chickens hatched, of these twenty-five were deformed and forty died during the first three or four days. Of the number unhatched, one-third were deformed, and 3 to 4 per cent had only developed a short way.<sup>3</sup>

Féré has experimented extensively with the influence of alcohol on the developing hen's egg. Alcohol was injected into the albumen in some experiments, while in others the eggs were placed under bell jars and exposed to the fumes of evaporating alcohol. Enough of the fumes penetrated the shell and entered the egg to affect the subsequent development of the embryos. When eggs were placed in the incubator after such

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3 These results by Ovize were taken from Forel's review

treatment they developed more slowly than the control and a large number of malformed embryos resulted. The abnormalities were variable, yet many had defective nervous systems and a number of the embryos exhibited eye defects. Féré made no attempt to analyze the cause of the different types of deformities, and in fact he paid little attention to the structure of the defects. Yet he showed most decidedly that alcohol fumes do affect the developing embryo, as one might have inferred from the preceding observations made by Ovize.

I have repeated Féré's experiments at some length during the past two years and can confirm his results. My object has been to regulate the treatment in such a manner as to get definite types of defects with certain intensities of treatment. Up to the present time I have only partially succeeded in doing this, though in several experiments the delay in development and the general type of the defects has been rather constant. This treatment of hen's eggs with alcoholic fumes is one of the most convincing and easily performed demonstrations of the influence of alcohol on development.

Féré also experimented with hen's eggs to show the influence of differences in temperature during incubation and many other physical and chemical factors. All unusual conditions affected the development of the embryo. Féré also developed hen's eggs in glass dishes after removing them from the shell. Preyer and Loisel had previously done similar experiments, but they carried the embryo for only a day or so, while Féré succeeded in keeping the egg developing for six days. Some of these embryos develop abnormally.

I have recorded a number of experiments on fishes' eggs which show the decided effects of alcohol and a large series of other substances on embryonic development. Alcohol and various anesthetics showed a peculiar affinity for the developing nervous system and organs of special sense. In many cases other organs and parts of the embryos were apparently normal. Many of the deformed individuals hatched and lived for some time, swimming about and feeding in a typical fashion.

With alcohol solutions of given strength definite defects were induced. In some experiments dozens of embryos with typical brain and eye defects occurred while few or no other types of deformities existed. *The experimenter has the power in these cases to predict with at least a limited degree of certainty the type of deformity which will result from a definite intensity of a particular treatment.* Embryonic development in such cases may really be regulated or controlled.

We have already considered a number of experiments on mammals which show that alcohol and other injurious substances affect the quality of the offspring. In the case of mammals the case is not so simple as in treating the eggs of lower animals, for the latter are more susceptible to the effects of alcohol and other substances.

parent's body. The effects in mammals may not be due directly to the substance used, but rather indirectly to the changed conditions the substances have induced in the body of the parent. It is important for this reason to know whether certain substances come in direct contact with the germ cells of the individual. As before mentioned, Nicloux and Renault have shown that alcohol may be readily found in the seminal fluid of a man shortly after drinking it. Thus the spermatozoa may come to float or swim in a weak solution of alcohol.

In the case of female mammals, Nicloux has carefully demonstrated the passage of alcohol from the blood of the mother into the tissues of the embryo. The following tabulation readily shows the results of his experiments on dogs and guinea-pigs.

TABLE 3.—PASSAGE OF ALCOHOL FROM THE MOTHER TO THE FETUS

		Amt of Abs Alc Inject per Kilo of Animal Weight, cc	Time of Absorption, Animal Killed, Hours	Amt Alc per 100 cc Maternal Blood, cc	Amt Alc per 100 cc Fetal Blood, cc	Amt Alc per 100 gm Mother's Liver, gm	Amt Alc per 100 gm Fetal Tissue, cc
1	Guinea-pig	5	5/6	0.36	0.31		
2	Guinea pig	5	1	0.47	0.35		
3	Guinea pig	2	1	0.20		0.10	0.12
4	Guinea pig	1	1	0.13		0.081	0.086
5	Guinea pig	0.5	1½	0.015		0.015	0.02
6	Dog	3	1½	0.37	0.37	0.26	0.26

After a short period of time the amount of alcohol in the blood of the fetus is about equal to that in the blood of the mother, while there is really more alcohol in a given weight of the tissues of the fetus than is to be found in an equal weight of liver tissues from the mother.

The reality of the passage of alcohol from the mother to the fetus demonstrates the possibility of the intoxication of the fetus. Therefore, nervous disorders, anesthesia, etc., of the late fetus may result as a consequence of alcohol in the blood, while the developing embryo or early fetus will show the effects by an abnormal formation of the nervous system.

Thus the results of the experiments of Maunet, Combemale and Hodge on dogs are readily explained as the direct influence of alcohol on the paternal germ cells in the case of the treated male, or on the developing fetus within the body of the alcoholic mother. The great number of human records briefly referred to above are also readily interpreted as the result of direct alcoholic action on the germ cells and the developing embryo.

The experiments on mammals do not then really differ greatly from those on the lower vertebrates where the externally developing eggs are placed directly in various unusual solutions, since the egg or embryo although within the mother's body is readily bathed or impregnated by the alcohol contained within the mother's blood.

The only experiments with alcohol on lower mammals which do not fall completely in line with the above records are those recently recorded by Nice. He has fed mice on alcohol. Each day 2 c.c. of 35 per cent alcohol was added to crackers and milk and placed as food for each mouse. Instead of drinking water the mice could drink 35 per cent alcohol from a syphon which prevented evaporation. Animals treated in this way gained in weight over the control. The offspring from these alcoholic mice excelled all the other mice in growth, even when they themselves were fed alcohol. The young grew faster, however, when not given alcohol. Nice treated other mice with tobacco fumes, nicotine and caffeine. The fecundity of the alcohol, nicotine and caffeine mice was greater than the control while those treated with tobacco fumes had almost twice as many young as the control. The mortality of the offspring from the treated mice was, however, greater than from the control. None of the control young died, while 17.3 per cent of the nicotine young and 11.1 per cent of the alcoholic young died soon after birth. There was only one abortion, no still-births and none of the young were deformed.

Mice may possibly be peculiarly resistant to these drugs, though I should rather think that in the case of alcohol, at least, the animals received too little to give a pronounced effect, though it was sufficient to cause a certain fatality among the young. Weak alcohol mixed with crackers and milk no doubt rapidly evaporates. The animals possibly waited until a certain amount of the alcohol had disappeared before they ate their food and of course, the amount of alcohol they took instead of drinking water was very small. Mice may easily be kept on a cracker and milk diet without ever receiving water. One cannot deny, however, that the mice did receive enough alcohol to cause them to fatten more rapidly than the control, and probably to cause the death of some of their offspring.

Caniere has shown that when guinea-pigs are inoculated with various soluble products of the tubercle bacillus for several months that the number of offspring is diminished. He sometimes observed the death of the fetus or premature death of the young while many of the living young had feeble constitutions. The action was produced when a parent was impregnated with the poison.

Mating together two inoculated animals gave 52 per cent of the living young. 28 per cent of the living young of the control animals were born.

only 20 per cent of the young survived. When the female alone was inoculated 26.9 per cent of the offspring were still-born, 34.6 per cent died under sixteen days and 38.4 per cent of the young survived. The matings with the male alone inoculated gave 16.6 per cent still-born, 10 per cent dying under sixteen days and 73 per cent of the offspring survived. Thus the effect of the toxin is shown on the germ cells of both sexes.

Lustig's experiments of inoculating fowls with abrin gave results parallel to those recorded by Carrière. The offspring were less resistant to inoculations of abrin, just as the guinea-pigs were to the tuberculosis extracts when compared with control animals of the same age.

Mall has clearly shown in his monograph on the causes of human monstrosities that poor nutrition and abnormal environment are most potent factors. Only 7 per cent of the uterine pregnancies examined gave monsters, while 96 per cent of the tubal pregnancies produced abnormal embryos.

Ballantyne has presented in his "Antenatal Pathology" a most comprehensive consideration of the part played by abnormal environment and disease in the causation of monstrosities and developmental defects in general.

The effects of malnutrition or poor environment on the developing embryo is splendidly illustrated by the case of monochoorial twins when one becomes more vigorous and pumps blood from the other through the anastomoses between their placental or umbilical vessels. In such cases one of the twins may fail to develop certain parts and may actually lack a heart, the heart of the superior embryo pumping blood through both the bodies. The various degrees of the degenerate or parasitic twin is thus produced. One individual falls behind in development and may finally actually be included within the body of the more vigorous twin. Double monsters may occur in which one individual is almost perfect, while the smaller monster is attached to some part of its body.

I have given this somewhat extensive survey of the literature in order to show that an abundance of evidence exists at the present time to indicate that the course of embryonic development may be readily modified. It is also clearly shown that the germ cells of various animals may be directly affected by different chemical treatments to such a degree that they give rise to defective individuals. The experiments of O. Hertwig and Morgan on the chemical production of spina bifida in large numbers of tadpoles and my experiments on the constant production of typical cyclopic monsters by subjecting developing fish eggs to definite chemical treatments strongly indicate that the manner of embryonic development may be definitely regulated. This exact regulation or control of development is the important goal of experimental teratology.

The problem is now in its beginning, since the actual influence of various treatments is known to be expressed in the resulting type of embryonic development.

The studies on alcoholism in mammals have failed to produce any convincing evidence of the specific actions of this poison. Yet the statistical studies on defective human beings would indicate that alcohol had a special affinity for the developing nervous system. My experiments on the influence of alcohol on the developing fish embryo demonstrated that alcohol did have a specific affinity for the central nervous system, and caused the brains of these embryos to exhibit numerous deformities while the organs of special sense were also affected.

#### METHOD AND RESULT

The experiments here recorded have been undertaken in order to ascertain whether alcohol did exert a marked influence on the germ cells and developing embryos of mammals, and, if possible to demonstrate the nature and mode of action of this influence. I have used alcohol as an agent, since it may be given to guinea-pigs without greatly disturbing their normal physiological processes, and so does not produce marked conditions which might secondarily affect the results. Alcohol may remain as such in the blood and tissues of a mammal, and so may act directly just as it would when added to the sea-water in which fishes eggs were developing. I have studied its effects experimentally on the eggs of lower vertebrates and am familiar with the defects it produces in these animals. It is an active substance and therefore, for these many reasons lends itself admirably to experimental use.

The experiments have been conducted on guinea-pigs since they breed fairly rapidly and rear their young without much difficulty in the laboratory. Strong healthy stock has been chosen and the animals have been carefully handled. All have remained in vigorous health and most of them have increased in size and fattened during the progress of the experiment. The males and females have been kept carefully separated and individual pairs mated from time to time.

The animals are first tested by normal matings and found to produce normal offspring. The alcoholic treatment is then begun on a given number of individuals and males and females mated in different combinations according to whether they are alcoholics or normal. An alcoholic male is mated with a normal female, the normal test. This is the crucial test for influence on the germ cells, since the defective offspring must be due to the chemically modified spermatozoa from which the male came, since the egg and the mother in which the embryo develops are normal.

Normal untreated males are paired with alcoholic females, the maternal test. Here the defective offspring may be due either to a modified ovum or to the fact that it developed in a mother with alcoholic blood, therefore supplying an unfavorable developmental environment. Lastly, its condition may be due to both of these causes. The mammalian mother has two chances to injure an offspring either by producing a defective egg, or secondly by supplying an unfavorable or diseased environment in which the embryo must develop.

The final combination is the mating of alcoholic individuals. This, of course, offers the greatest chance for defective offspring.

Alcohol is administered to the guinea-pigs by inhalation. At first it was given with the food, but the animals did not relish it, and therefore took less food. It was then given by stomach tube, but this method

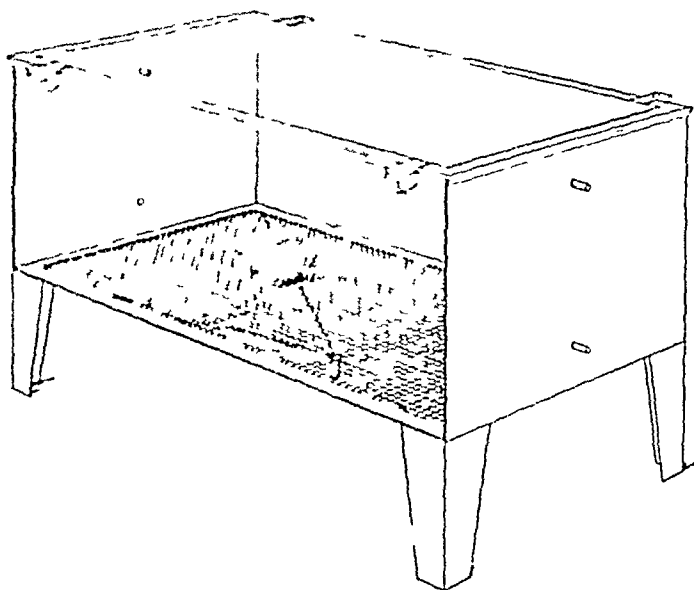


Fig 1—Tank for alcohol treatment. Animals are placed on the wire screen in the closed tank and inhale the fumes of alcohol evaporating from the cotton below the screen.

so upset the animals that the results might have been modified by their poor bodily condition and the bad state of their stomachs. The inhalation method is entirely satisfactory, the guinea-pigs thrive and usually gain in weight during the experiment, they have good appetites and are in all respects apparently normal. The only indication of the effects of the treatment is shown by the quality of offspring they produce.

The apparatus used for giving the alcohol consists of an air-tight copper tank 36 inches long by 18 inches wide and 12 inches deep, with a sloping bottom draining to the center. Over this bottom is placed a wire screen and below the screen cotton soaked with 95 per cent alcohol is spread (Fig 1). The tank is closed and allowed to stand until the





The majority of them sit quite motionless and sniff their noses for a time and then become somewhat drowsy. A few individuals, however, are excited by the treatment and run about the tank, becoming sexually excited, and many often fight other animals savagely. One of the males fights and bites so vigorously while taking the fumes that he has to be treated separately from all others. The fumes then have a different influence on the behavior of different individuals in much the same way that alcoholic intoxication expresses itself differently on different human beings.

During the first few weeks of the treatment the fumes cause the eyes to water so that tears run over the face. The nose and mouth also become moist and the animals sniff almost constantly. The fumes are very irritating to the mucous membranes at first. The cornea becomes irritated and finally opaque in some instances so that the eye takes on a white appearance. The tissues seem, however, to develop a resistance to the fumes. The eyes become clear after a few months and never again become opaque. The nasal mucosa also ceases to secrete excessively unless the animal is left in for an unusually long time.

Many of the guinea-pigs have been killed after treatments of different duration up to fifteen months and all of their viscera carefully examined. In no case have I found any changed structures due to the alcoholic treatment. The lungs, liver, stomach, intestines, kidneys, reproductive glands, brain and all other parts appear perfectly normal. The general health and behavior of the animals also indicate that they are in good condition. As before mentioned, several animals have been partially castrated during the experiment. One of the reproductive glands was removed and examined microscopically. In all cases the germ cells, ova or spermatozoa as the case may be, were found to exhibit perfectly normal structure. One cannot claim, therefore, that this treatment is excessively severe or greater in proportional amount than the alcohol a human being often takes. The fact is that these animals have never been completely intoxicated, but receive only enough alcohol six times per week to affect their nervous states. They may be compared to a toper who drinks daily but never becomes really drunk.

While the bodies of these animals display no direct effects of the alcohol, the conditions of the offspring to which they give rise show most strikingly the effects of the alcoholic treatment. The results of mating the alcoholized guinea-pigs are summarized in Table 4.

Fifty-five matings of treated animals have been made. Forty-two of these have now reached full term and are recorded. Thirteen matings are not yet due. From the forty-two matings only seven young survived, and six of these are still living, five of which are runts, though their parents were unusually large, strong animals (Figs. 4 and 5).

The conditions of the animals in the mating pairs are shown in the first column of the table and the total results of the matings are indicated in the following columns. The first horizontal line gives the records when alcoholic males are paired with normal females. Twenty-four such matings were made. Fourteen of these gave negative results, or resulted in early abortions. Many embryos were aborted during very young stages, and some of these were deformed, though they were generally in such poor condition after being cast out into the cages that little could be learned from them. They were partially or completely eaten by the mother in most cases. The males were always kept for a number of days with the females during favorable periods, and conception should have occurred in all cases, as it did in the control matings.

TABLE 4—EFFECTS OF ALCOHOL ON OFFSPRING OF GUINEA-PIGS

Condition of Animal	No of Matings	No Result or Early Abortion	Still Born Litters	No Still-Born Young	Living Litters	Young Dying Soon After Birth	Surviving Young
Alcoholic male by normal female	24	14	5	8	5	7	5'
Normal male by alcoholic female	4	1	0	0	3	3 (a)	2†
Alcoholic male by alcoholic female	14	10	3	6	1	1 (b)	0
Summary	42	25	8	14	9	11	7‡
Normal male by normal female—Control	9§	0	0	0	9	0	17

\*Four survivors in one litter and one was a member of a litter of three the other two died immediately after birth. (a) Premature (b) Sixth day.

†One lived to become pregnant with two young *in utero*, one deformed, Fig. 3. Other survivor normal, the mother was not treated until after first two or three weeks of pregnancy.

‡Of thirty-two young born only seven have survived.

§One other non alcoholic mating was made from which two young resulted, they died after the second and fourth days, respectively and the mother died two days later, her diseased condition no doubt affected the suckling young. They have for this reason not been included in the normal control.

Only ten of the twenty-four matings resulted in conceptions which ran the full term. Half of these, or five, were still-born litters. There were three still-born litters of two young each and two of one individual each. Most of these were slightly premature, their eyes being closed and the hair sparse on the bodies. (A normal guinea-pig at birth is well covered with a hairy coat, its eyes are open and it very quickly begins to run about actively.)

The only other survivor from an alcoholic mother is strong and full grown for its age. The mother had been treated for only two and one-half months when the offspring was born, so that she was normal during the first two or three weeks of pregnancy. No doubt the early stages of development are more easily modified to produce significant defects than are the later. This question is being more fully tested on guinea-pigs with experiments now in progress. I have shown, however, in

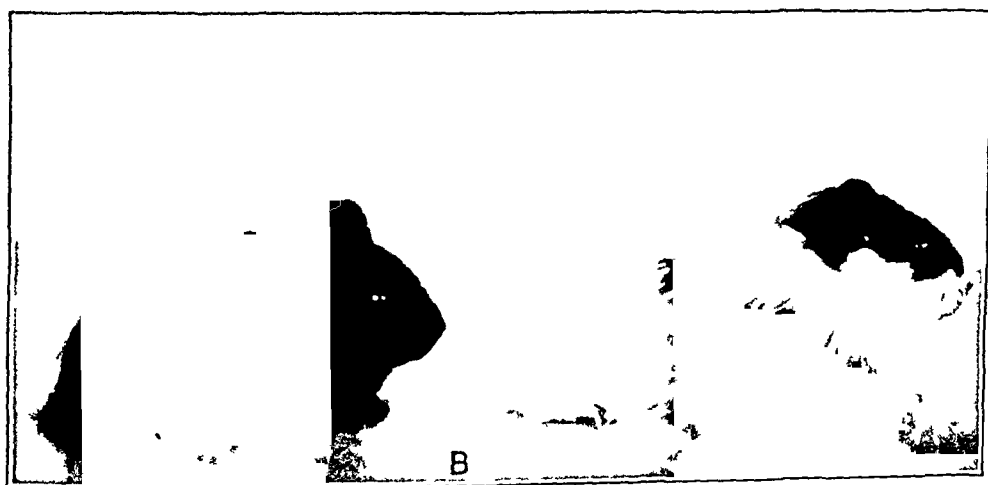


Fig. 1—A The animal on the left is a runt from a large alcoholic male and a large normal female weighs 134 gm. The animal on the right, from normal parents, is larger although 1 month younger and weighs 147 gm.

B The guinea pig on the left is a runt weighing 132 gm from an alcoholic father, on the right a normal guinea pig twice as large though only 10 days older, weighs 221 gm.

treating fish eggs that the period at which the treatment is applied is a most important factor in determining the type of defect or modification which will result. Certain salts, different strengths of magnesium chloride, for example, which give pronounced effects when added to the

sea-water containing eggs in early developmental stages, may really be ineffective after the eggs have developed beyond these stages. In the case under consideration the offspring might not have fared so well if the alcoholic treatment had been started on the mother a few weeks before conception, instead of three weeks after her pregnancy had begun. This with other points shall be more completely analyzed in future communications on these experiments.

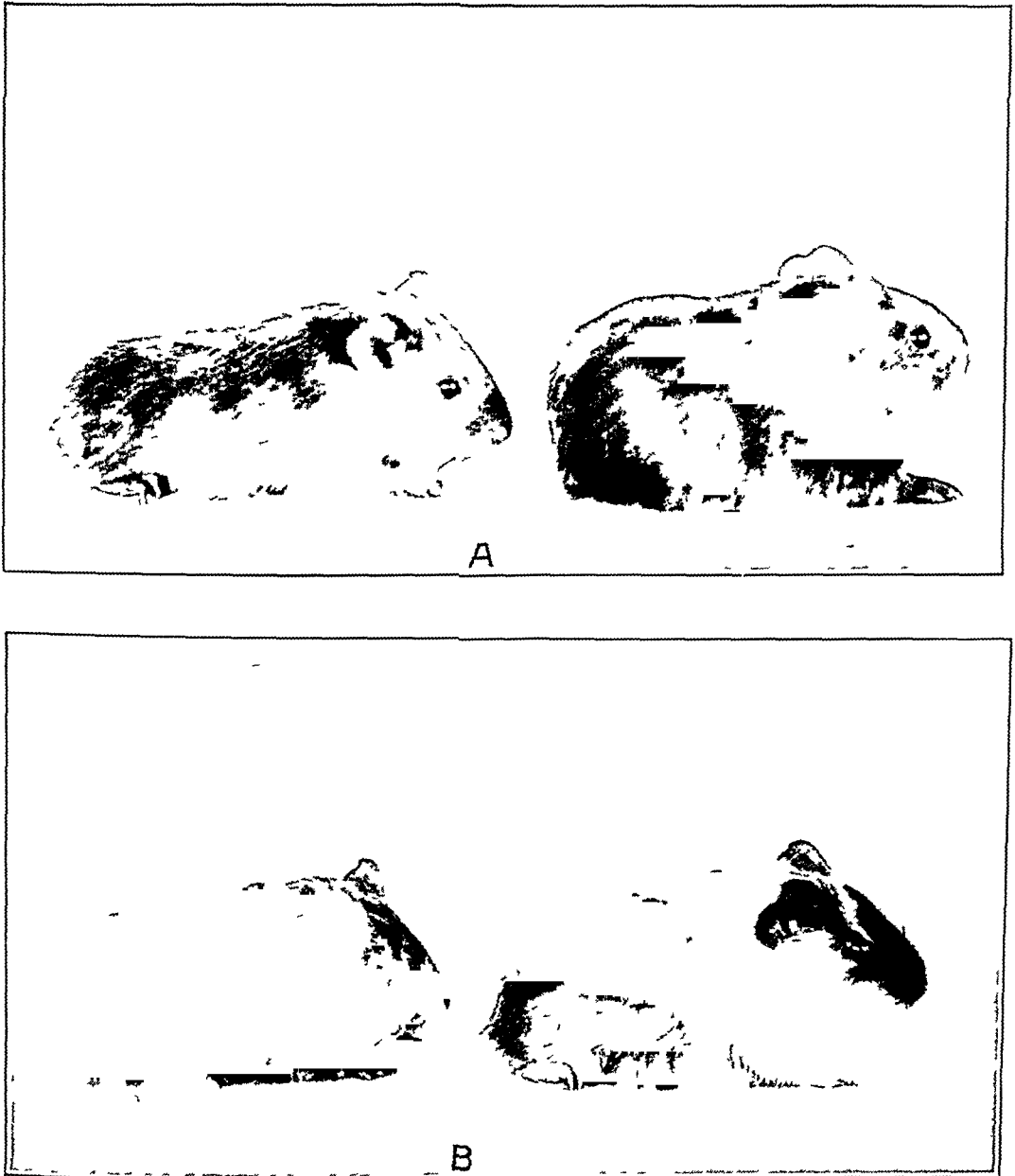


Fig 5—A Two guinea pigs from alcoholic fathers, the left one 1 month and 10 days younger than the runt on the right

B The left animal is the same as above, the right another of the same runt litter

The four matings of alcoholic females and normal males resulted in three living litters in all of five individuals. Three of the young were premature and died shortly after birth, while two young survived.

Finally, we may consider the results of pairing two alcoholized individuals. The third line of the table summarizes these results. As might have been anticipated, this type of mating has given the highest fatality of all.

Ten out of a total of fourteen matings have given no offspring or early abortions, which were in many cases eaten by the mother. Three still-born litters have been produced, each consisting of two young. *Only one living litter was born from the fourteen matings in which both parents were alcoholic and this litter consisted of but one weak individual which died in convulsions on the sixth day after birth.* This is indeed a decided effect of alcohol on the offspring when one compares it with nine control matings all of which gave living litters containing a total of seventeen individuals all surviving.

Two other young were produced by non-alcoholic parents and died on the second and fourth days after birth. They have not been included in the control since the mother died two days later in a diseased condition. No doubt the poor state of the mother had much to do with the fate of the suckling young. She was an animal that had only been in the experiment for a short time and is one of the very few that have contracted disease or died during the nineteen months of the work. This might possibly go to show the influence of a diseased mother on the offspring.

The fourth line of Table 1 gives a summary of the experiments. There have been forty-two full-term matings, twenty-five of which gave no results or early abortions, eight still-born litters have occurred, consisting of fourteen individuals, only nine living litters have been born, 21 per cent. of the matings. These contained eighteen young, and but seven of this number have survived and five of these survivors are unusually small (Figs. 4, 5).

The bottom line of the table shows nine control matings. All have given living litters containing a total of seventeen young, all of them surviving. The two young that died as stated above were from a dying mother and not included in the control.

Records of the successive matings of ten of the female guinea-pigs are shown in Table 5. The varying ways in which the same individual has responded in different matings is noticeable. Number 10, an alcoholic female, first mated with an alcoholic male gave one young which died on the sixth day after birth. On being remated with the same male, No. 10, gave no result. When mated with another alcoholic male gave no result. She mated again after several months with the first male and on being killed was found to contain one embryo *in utero* about 2 weeks old.

Female 15, a normal guinea-pig, shows an instructive record. She was mated with an alcoholic male and gave birth to two still-born young.

When mated with another alcoholic male she gave a negative result. Remated with the second male she gave two young, both of which died of convulsions within four weeks after birth. She was then mated with a normal male as a control and gave one vigorous normal offspring which survived.

TABLE 5—RESULTS OF SUCCESSIVE MATINGS OF TEN FEMALES

Animal	First Mating	Second Mating	Third Mating	Fourth Mating
No 10 Alc	Alc male 4, 1 young died in 6 days	Alc male 4 0	Alc male 6 0	Alc male 4, 1 embryo in utero 2 weeks after
No 12 Alc	Alc male 5 0	Alc male 5 0	Alc male 4 0	
No 11 Alc	Alc male 6 0	Alc male 6 0	Alc male 5, 2 prenat still-born	Alc male 4 0
No 13 Nor	Alc male 5 1 still-born	Alc male 5 0	Alc male 4 0	
No 17 Nor	Etherized male 1 0	Etherized male 1 0		
No 18 Nor	Alc male 5 0	Alc male 5 0	Alc male 6 0	
No 7 Nor	Etherized male 2, 2 prenat still-born	Etherized male 2 0	Etherized male 2 0	
No 14 Nor	Etherized male 3 0	Etherized male 3 0		
No 19 Nor	Alc male 4 0	Alc male 6, 1 still born	Alc male 6 0	Alc male 5, 4 small, active, only one half size, but living
No 15 Nor	Alc male 6, 2 still born	Alc male 5 0	Alc male 5, 2 died fourth week of convulsions	Nor male, 1 normal vigorous young

The other records are easily understood.

These experiments have suggested many questions still to be solved, some of which are now being tested, such as the length of time necessary to treat an animal before the resulting offspring is affected, whether this time is equally long for both sexes, and what amount of individual variation may exist. An important point to ascertain is whether the effects of the alcohol treatment are permanent, or does the animal recover after a time and again become capable of giving normal offspring. One of the most valuable problems is to regulate the treatment in such a manner as to induce a definite type of defect with a given kind or degree of treatment. The structure or morphology of the monsters and defective

offspring which occur is to be carefully studied. Many other points might readily be suggested.

Definite and well-controlled experiments with alcohol and other substances on the mammalian offspring have not been sufficiently studied. The work is really in its beginning, and while there is much evidence to show that various toxic agents do affect and modify the offspring facts are badly needed to demonstrate the regularity and manner of this modification. The present experiments seem to me to prove in a convincing way that alcohol may readily affect the offspring through either parent and that this effect is almost fatal to the existence of the offspring when the parents have been treated with even fairly large doses of alcohol. Many of the cases seem to indicate further that the tissues of the nervous system of the offspring are particularly sensitive in their responses to the induced conditions.

My assistant, Miss Craig, has aided me greatly throughout almost the entire progress of these experiments. Last year during my absence abroad she assumed entire control of the animals and I am indebted to her for this efficient assistance.

#### SUMMARY

Ginea-pigs have been treated with alcohol in order to test the influence of such treatment on their offspring. Male and female animals are given alcohol by an inhalation method until they begin to show signs of intoxication though they are never completely intoxicated. They are treated for about an hour at the time six days per week. The treatment in some of the cases has now extended over a period of nineteen months. The animals may be said to be in a state of chronic alcoholism.

Fifty-five matings of the alcoholized animals have been made, forty-two of which have reached full term and are recorded.

From these forty-two matings only seven young animals have survived and five of them are unusually small though their parents were large vigorous guinea-pigs. The following combinations were made:

1. Alcoholic males were mated to normal females. This is the paternal test, and is the really crucial proof of the influence of alcohol on the germ cells, since the defective offspring in this case must be due to the modified spermatozoa or male germ cells from which they arise. Twenty-four matings of this type were made, fourteen of which gave no result or very early abortions, five still-born litters were produced, consisting of eight individuals in all, and five living litters containing twelve young. Seven of these twelve died soon after birth and only five have survived. Four of the survivors are from one litter and the fifth is the only living member of a litter of three.

2. Normal males were mated with alcoholic females. This is the maternal test. In such cases the alcohol may affect the offspring in two ways—by modifying the germ cells of the mother or acting directly on

the developing embryo *in utero*. Only four such matings were tried. One gave no offspring, three living litters were born, one consisting of three premature young that died at birth, while the other two litters consisted each of one young, which have survived. The alcoholic treatment in one of the last cases was only begun after the mother had been pregnant for about three weeks.

3. Alcoholic males were mated to alcoholic females. This is the most severe test, both parents being alcoholic. Fourteen such matings gave in ten cases no offspring, or very early abortions. Three still-born litters were produced, consisting in all of six individuals, while only one living young was born. *This single offspring from the fourteen matings died in convulsions on the sixth day after birth.*

The young that have died in the experiment showed nervous disorders, many having epileptic-like seizures, and all died in convulsions.

*Nine control matings in the same group of animals have given nine living litters*, consisting in all of seventeen individuals, all of which have survived and are large, vigorous animals for their ages. Two young from non-alcoholic parents died, but this mother also died two days later. Her diseased condition doubtless affected the suckling young.

*Forty-two matings of alcoholic quinea-pigs have given only eighteen young born alive, and of these only seven, five of which are runts, survived for more than a few weeks, while nine control matings have given seventeen young, all of which have survived and are normal, vigorous individuals.* These facts convincingly demonstrate the detrimental effects of alcohol on the parental germ cells and the developing offspring.

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# PROGRESSIVE INTERSTITIAL HYPERTROPHIC NEURITIS OF CHILDHOOD OF DEJERINE AND SOTTAS REPORT OF A CASE<sup>1</sup>

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This rare disease was first described as an independent affection by Dejerine and Sottas<sup>1</sup>. Previous to their publication Gombault and Mallet<sup>2</sup> published the account of an observation of a patient having the characteristics of this affection but they considered it as a case of tabes. There are but three autopsies recorded, those of Dejerine and Sottas,<sup>1</sup> of Dejerine and Thomas<sup>3</sup> and the case of Pierre Marie studied by Boveri<sup>4</sup>.

This disease has been studied chiefly in France. The original descriptions of Gombault and Mallet, Dejerine and Sottas and a subsequent publication by Dejerine<sup>5</sup> give a complete and thorough description of the affection from a pathological as well as a clinical standpoint. A good account is found in the work of Dejerine and Thomas,<sup>6</sup> and it is briefly considered by Pierre Marie<sup>7</sup> in his book on neurology. Short accounts are also found in v Hutinel's System,<sup>8</sup> in the work of Pfaundler and Schlossmann<sup>9</sup> and in Osler's Modern Medicine<sup>10</sup>. Sainton<sup>11</sup> takes up the question of differential diagnosis and holds very strongly for the independent classification of the affection. This has been brought in question by Marinesco,<sup>12</sup> Beduschi<sup>13</sup> and Raymond,<sup>14</sup> who believe that the affection is

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1 Dejerine and Sottas Soc biol, séance du 18 mai 1893 Mem Soc de biol, 5, 9 séries 1893, p 63

2 Gombault et Mallet Un cas de tabès avant débuté dans l'enfance Autopsie Arch de méd expér 1889, p 385, pl x

3 Dejerine and Thomas Soc neurol, June 5 1902 Quoted by Marie in La Pratique Neurologique

4 Piero Boveri Munchen Med Wehnsch, June 6, 1911, p 1238

5 Dejerine Rev de méd, November, 1896, xvi

6 Dejerine and Thomas Maladies de la Moelle Epinière, Paris, 1909

7 Marie, Pierre La Pratique Neurol, Paris, 1911, p 696

8 v Hutinel Les Maladies des Enfants Paris, 1909, v, 426

9 Pfaundler and Schlossmann Handbuch der Kinderheilkunde Leipzig, 1910, 4 Band, S 173

10 Osler's Modern Medicine Philadelphia, 1903, vii, 113

11 Sainton Thèse de Paris 1889 Quoted by Dejerine, Mal de la Moelle Ep, p 776

12 Marinesco Arch de path expér et comparée, 1895, quoted by v Hutinel

13 Beduschi Riv di patholog nervs ment, 1906, quoted by v Hutinel

14 Raymond Cliniques, 1903, quoted by v Hutinel

identical with or forms a type of, the myelopathic muscular atrophy type Charcot-Marie Dejerne Sanion, Pierre Marie and Boveri hold for the independence of the affection and claim that the hypertrophy of the nerves, which constitutes one of the most striking characteristics of the disease is an early pathological finding and not a late development accompanying muscular atrophy and deformity. I believe that the case that I am to report will throw some light on this question.

In Germany, Brasch<sup>15</sup> presented two doubtful cases in Berlin in 1903 which he believed to be subforms of this disease. There was, however, no distinct hypertrophy of the peripheral nerves in his cases and in the discussion which followed Remak thought that they fell rather into the classification of the type of muscular atrophy described by Hoffmann of Heidelberg (progressive neural muscular atrophy).

#### DESCRIPTION OF DISEASE

It has its commencement in childhood between the eighth and fourteenth year and is frequently a family affection. It is characterized by a progressive course by ataxia, by muscular atrophy and a marked disturbance of the sensibility together with hypertrophy of the nerve trunks which is the distinguishing feature of the disease. The muscular atrophy commences in the extremities and the inferior extremity is always involved before the superior. The atrophy of the small muscles of the hands is of the Aran-Duchenne type. The atrophy and the malformation of the feet is such as is met with in Friedreich's ataxia. Fibrillary contractions of the muscles have been occasionally noted. The cutaneous and tendinous reflexes are abolished. The muscular response to the faradic and galvanic currents is diminished. Reaction of degeneration is occasionally noted. All forms of sensibility are markedly affected. The walk is that of steppage, but not typically so, as the presence of a certain amount of ataxia produces a very unsteady gait. The sign of Romberg is present and there is a marked ataxia in the finger-nose and heel-knee tests. The reaction of the pupil to light is slowed or entirely absent while the reactions to accommodation and to convergence are conserved. Thus the Argyll Robertson pupil has been observed. The sphincters are intact. The hypertrophy of the nerves is perhaps the most striking feature of the clinical picture. Not only are the great nerve trunks of the extremities involved, but also the cutaneous branches. To quote the description of Dejerne

It is a uniform hypertrophy without nodosity or any unevenness, the consistency of the nerves is greatly increased and gives to the palpating finger the impression of the arteries of a cadaver previously injected with gelatin. The pressure on the nerve trunks, even though it be great, causes no pain. In the hypertrophic interstitial neuritis there is a veritable analgesia of the nerve trunks to pressure and to the electric current.

<sup>15</sup> Brasch. Berlin Gesellsch. f. Psychiat. u. Nervenkr., July 13, 1903. Reported in Neurol. Centralbl., 1903, No. 15, p. 748.

Due to the atrophy of the muscles which tend to support the spinal column kyphoscoliosis has been noted Exophthalmos, scanning speech, intention tremor and nystagmus may be present

Bovey<sup>4</sup> has described two clinical types of the affection

1 *Type Gombault-Dejerine-Sottas*—Myosis, Argyll Robertson pupils, lightning pains, motor ataxia, fibrillary twitchings, nystagmus, absence of intention tremor, of scanning speech and of exophthalmos and the presence of general muscular atrophy

2 *Type Pierre Marie*—No true Romberg, no myosis, no true Argyll Robertson pupils, only slow reaction to light, no lightning pains, motor ataxia, nystagmus or fibrillary twitchings Intention tremor, scanning speech and exophthalmos present Muscular atrophy limited to the lower extremity and barely indicated in the hands This type therefore presents points of similarity to multiple sclerosis.

#### PATHOLOGICAL ANATOMY (DEJERINE)

The cranial nerves are larger than those of a normal individual, but are far less hypertrophied than the spinal nerves The sympathetic system takes a prominent part in the hypertrophy The ganglia of the posterior roots are notably enlarged The spinal cord is not altered in volume, but there is an atrophy of the posterior columns and an accompanying leptomeningitis in this locality The dura mater about the cord is not altered Histologically, the nerves show both interstitial and parenchymatous changes The interstitial changes are typical The proliferation of fibrous tissue instead of taking place between the nervous elements in the endoneurium, as in certain other forms of neuritis, takes place about the individual nerve fiber or about several fibers forming an isolating sheath, without, however, the endoneurium being affected This sheath of connective tissue is disposed concentrically about the nerve fiber much after the fashion of the layers of an onion In the peripheral nerves one sees few nuclei, on the contrary the spinal roots show abundant nuclei of the embryonic type and vacuoles are numerous The posterior horns of the gray matter in the cord are small The cells of the anterior horn studied by Nissl's method show a diminution in number and some are found atrophied and the chromatic network is hardly visible

#### DIFFERENTIAL DIAGNOSIS

This affection must be differentiated from the Charcot-Marie type of spinal muscular atrophy, from Friedreich's ataxia, from an ordinary peripheral neuritis and from juvenile tabes I saw a case in the service of Pierre Marie in Bicetre, which was considered to be a case of Friedreich's ataxia until the discovery of the hypertrophic nerves showed the error in diagnosis The first described case of this affection was classed as a juvenile tabes The case I have to report resembles tabes very much in its clinical aspect The following is the report of the case

## CASE REPORT

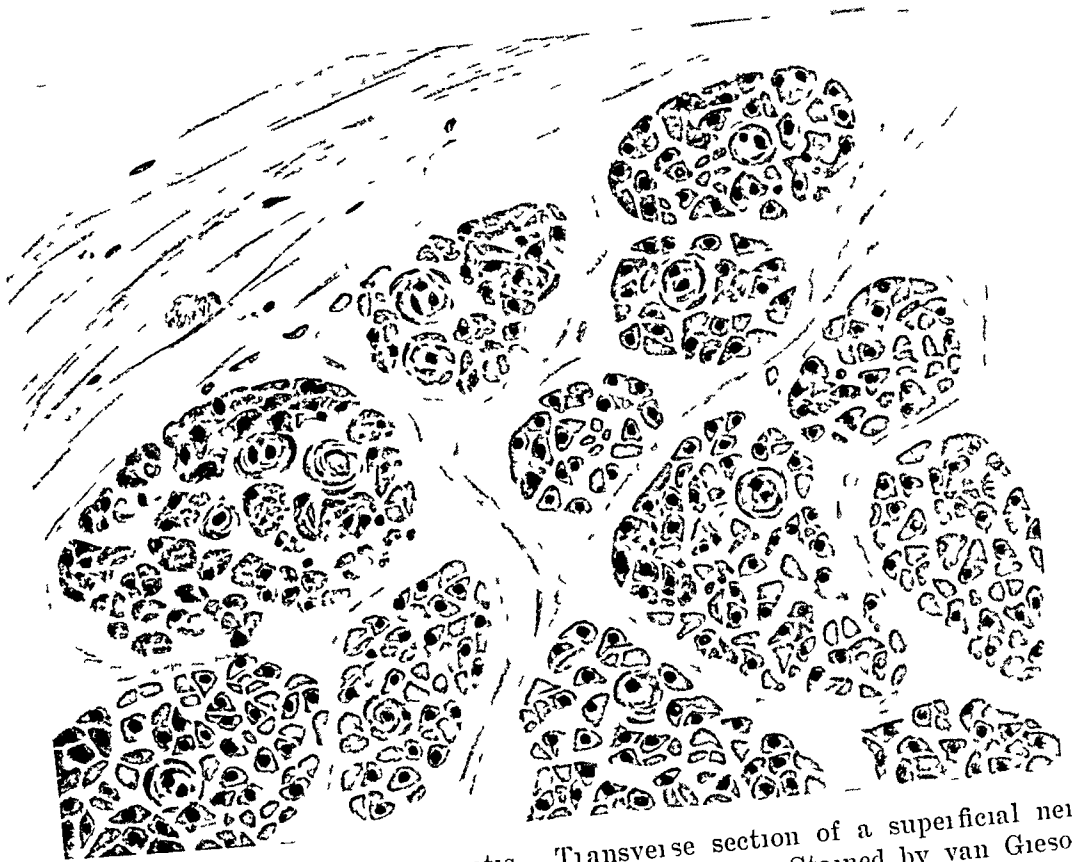
A B, aged 20, native of San Francisco, of German parentage, newsboy, came to the out patient clinic in January, 1912 complaining of trouble in walking, and of weakness.

*Family History*—Father and mother living and well. The mother gave no history of abortion or miscarriage. The patient has two sisters both of whom are well. An examination of these sisters as well as of the mother presented no evidence of the disease in any one of them. The father was not examined, but he is said to be in good health, and there was no history of a similar affection being present in any branch of the family.

*Precious History*—The birth was normal and the infant was normal in every respect. He was fed at the breast for a period of nine months. Dentition commenced at five months. He began walking at 13 months and began to talk at 2 years of age. He had measles, whooping cough and chicken pox between the seventh and the ninth years.

*Present History*—The present trouble began seven years prior to this report when he was seized with an attack of general weakness and loss of ambition. The mother thinks the illness commenced from bathing in a contaminated swimming pool. Other children in the vicinity became sick from this same cause she thinks. Some took typhoid fever and others had diphtheria. At the onset of his trouble fever was not present and a doctor was not consulted until several months later. At this time failing strength was noticed which first began in the legs and extended to the arms and hands. This advanced to such a stage that he could not care for himself. There was no trouble with the sphincters. The doctor whom he consulted prescribed a Kneipp water cure. Patient states that while under this treatment he improved slowly for one year. After 1906, the patient's condition remained about the same until September, 1911, since which time the trouble has become worse. The principal complaint of the patient is that the legs feel heavy and get tired easily and that he is unsteady on his feet. He never has had pain. He has difficulty in performing the finer manipulations, such as buttoning his coat and tying his tie. Writing has become difficult and unsteady. There is no disturbance in articulation or deglutition. The sphincters function normally. Sight and hearing are unaffected and the mentality has in no wise suffered. The speech is slow and measured, but the mother states that this has always been so. There is no complaint of headache, vomiting or dizziness. The appetite is good. Constipation is apt to be the rule. The weight has not varied of late, there is no cough or night sweats. Patient leads a very quiet moderate life, living with his parents. Denies all venereal infection and does not use tobacco or indulge in alcohol.

Status, January 26, 1912—A fairly well nourished young man below the average height. Weight 115½ pounds. Pulse 78 regular and of good volume and tension. The face presents a sallow and rather bloated appearance with puffiness about the eyes. The neck is very broad and thick set. The upper lip is somewhat projected, the labial commissure is transverse and the smile is transverse. There are numerous moles about the face. The spine shows a moderate lateral scoliosis. There are several patches of pityriasis versicolor on the chest. The tongue is hypertrophied, the hypertrophy being of the entire organ and also of the individual papillae, there is a scattered but well marked exfoliating dermatitis present, shown by numerous slightly elevated patches with a fine sinuous border, forming an incomplete ring. These patches change their position from day to day. No scars suspicious of syphilis are seen on the surface of the body or in the nasopharynx. The tonsils are enlarged. There is no noticeable atrophy of any of the muscles. There is no superficial glandular enlargement. No trembling of the hands. The strength in the hands is diminished. Dynamometer readings right hand 22 kg, left hand 22 kg (pressure). The power in the arms, forearms, legs and thighs is fairly well conserved, but the flexors of the foot are decidedly weak while the extensors are not so affected. The walk is that of the steppage gait with at the same time an ataxia and a certain incoordination and swaying. In the pointing movements of the hands and of the feet there is some error when the eyes are open, and this is much increased when the eyes are closed. There



Hypertrophic interstitial neuritis Transverse section of a superficial nerve of the cervical plexus measuring 3.5 mm in diameter Stained by van Gieson's method The individual nerve fiber is seen surrounded by a sheath of connective tissue consisting of a number of layers disposed concentrically



is some adiadochokinesis in both hands, but this is not pronounced. There is a distinct Romberg, but no asynergia or "*mouvements démesurés*" (Babinski).

**Reflexes** The knee jerks, ankle jerks and radial reflexes are absent. The triceps reflex is present. The abdominal reflexes are present and the plantar reflex is in flexion. The anal and cremasteric reflexes are absent. On percussion of the muscles the muscular reflex is everywhere present.

**Sensibility** The sensibility is markedly affected in the extremities but not about the trunk. The sensibility to touch, to heat and cold, and to pain shows a diminution which is more pronounced at the periphery of a member than at its base. The deep sensibility is likewise affected. The pressure sense, sense of position, notion of the position of the segments of a member, including the muscular and articular sensibility, and the osseous sensibility, are impaired. There is a disturbance of the stereognostic sense. Pallesthesia as tested with the Luer fork shows perception of the vibration between 6 and 7 over the lower radius and ulna and 5 plus over the internal malleolus—figures considerably below the normal.

**Hypertrophy of the nerves** The nerve trunks of the axilla, the ulnar nerve at the bend of the elbow, superficial branches of the cervical plexus, cutaneous branches on the dorsal surface of the forearms and the external popliteal nerve are markedly hypertrophic and easily palpable. They are not sensitive to pressure and on palpation are found to be free from unevenness and may be rolled under the finger like a sclerotic artery. The ulnar nerve at the bend of the elbow feels about the size of a large goose quill.

**Ulnar Nerve Reflex** If the patient be placed in the anatomical position with the palms of the hands anteriorly and the arm be percussed above the olecranon at the inner side, a brusque movement of pronation takes place due to the percussion of the enlarged ulnar nerve and the consequent contraction of the flexor carpi ulnaris. This is found constantly on the left side.

**Ocular Nerves** The pupils react well to light and accommodation, are equal in size and regular in contour. The eye movements are normal, there is no contraction of the field of vision and no nystagmus. Report from the eye clinic "Disks pale in color but normal." Taste and smell are normal. No anesthesia about the distribution of the fifth nerve and no involvement of the facial nerve. Sense of hearing is acute in both ears. The corneal and pharyngeal reflexes are both present. The tongue is not deviated from the mid-line but there is a slight trembling. No trouble in deglutition or articulation.

**Electrical Reactions of the Muscles** The electrical reactions of the muscles show an alteration consisting of a hypo-excitability to both the faradic and galvanic currents. In certain muscles an incomplete reaction of degeneration is found. Thus in the extensor communis digitorum and the extensor longus digitorum there is a decided slowing of the contraction to the galvanic current with inversion of the formula ACC being greater than KCC. In the trapezius, deltoid, biceps, triceps, flexor profundus digitorum, first dorsal interosseus of the hand, biceps femoris, quadriceps femoris, tibialis anticus and flexor longus digitorum there is no inversion but a slight slowing of the contraction, not so marked as in the case of the extensors, where the contraction is almost vermicular.

In the supinator longus, peronei, flexor longus hallucis, extensor proprius hallucis, semimembranosus, semitendinosus, gastrocnemius and soleus the contraction is quick. In every case the faradic excitability is conserved.

An examination of the heart, lungs and abdomen shows normal conditions. The liver is not enlarged and the spleen cannot be palpated. Over the body generally the muscles give a sense of increased tonicity. No fibrillary twitchings of the muscles are observed. The urine shows no albumin nor sugar and a microscopical examination of the sediment shows no casts.



Blood Red cell count, 4,350,000, white cell count, 4,600 Hemoglobin, 96 per cent, color index, 89 per cent Differential white count, polymorphonuclear leukocytes, 58 per cent, lymphocytes, 40 per cent, large mononuclear leukocytes, 2 per cent Wassermann reaction in the blood negative

**Microscopical Examination of an Excised Nerve** One of the enlarged superficial cervical nerves was excised for microscopical examination This nerve, which was visible beneath the integument, measured 3.5 mm in diameter in the fresh specimen Stained sections showed the typical picture of interstitial connective tissue proliferation about the individual nerve fiber In one place in the specimen, not pictured in the illustration, there is a proliferation of the endoneurium with round-cell infiltration, but this is not characteristic of the general appearance of the specimen The following is the report of the pathologist, Prof William Ophuls

Cross sections through the nerve show a moderate fibrous thickening of the perineurium There is also in places quite a marked round cell infiltration of the nerve itself with diffuse thickening of the endoneurium Around many of the nerve fibers the sheath of Henle is thickened which has led to the formation of concentric masses of connective tissue around them Diagnosis, chronic interstitial hypertrophic neuritis

#### TREATMENT

Under arsenic in the form of Fowler's solution in moderate doses and the employment of the constant galvanic current, considerable improvement was obtained It is probable, however, considering the chronic and progressive character of the disease, that this improvement is only temporary, but its course may extend over many years and the prognosis as far as life is concerned is good

#### DISCUSSION

The beginning of the affection in childhood, the marked hypertrophy of the nerves, the ataxia, the loss of muscular strength, the change in character of the electrical muscular reactions, the marked disturbance of the sensibility and the histopathological findings in the hypertrophied nerve fiber itself establishes the diagnosis of this case on a clinical as well as pathological basis The process is evidently in the early stages, as a number of symptoms such as the atrophy of the muscles, Argyll Robertson pupils and deformity, which may develop at a later stage, are now absent In this connection I wish to emphasize the early and great hypertrophy of the nerve trunks, for some have held that this occurs only in the later stages of the condition or even go further and believe that in the presence of a marked atrophy the nerve trunks stand out more prominently and are not really hypertrophied, but only apparently so From our observation of this case this hypertrophy of the nerve trunks which surpasses that seen in two other cases much more advanced, leads us to believe that it plays an important part in the clinical picture, and to hold with Dejerine and others that we have to deal here with a distinct affection

## THE INFLUENCE OF RADIUM AND OF ITS DECOMPOSITION PRODUCTS ON THE FERMENTS \*

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Recently radium, its emanations and the products of its decomposition or breaking-down have been coming more and more into consideration as therapeutic agents, not only in skin diseases and diseases with cutaneous manifestations, but also in various "internal diseases" of the most diversified nature, especially carcinoma and the arthritides, and as this interest seems distinctly on the increase and there seems to be a real hope that in some, at least, of these diseases a cure may be obtained by this means, it would seem of interest to know the exact effect of certain salts or products of radium on those substances of such vital importance to the body metabolism — the ferments.

As a slight contribution to this subject we have carried on a series of experiments on the effects of Radium-Lead, Radium D, E and F from radio-active ores, and Radium D, obtained from emanations, on certain of the ferments of the body, choosing as fair examples the proteolytic ferment of the stomach, pepsin, the diastatic ferment of the pancreas and the so-called autolytic ferment of the liver. These experiments have been done *in vitro* and are, of course, open to the criticism which may be applied to all such experiments when one attempts to apply them *in vivo*.

It will be remembered that radium gives off three kinds of rays,  $\alpha$ ,  $\beta$  and  $\gamma$ , radium itself giving off  $x$ -rays and changing into gaseous emanations, these in turn giving off  $x$ -rays and changing into Radium A, which changes into Radium B, and this into Radium C, giving off  $\alpha$ ,  $\beta$  and  $\gamma$  rays, the Radium C changing into Radium D, and this in turn after giving off  $\beta$  and  $\gamma$  rays into Radium E, which finally gives off  $x$ -rays and changes into Radium F. Radium itself lasts many years — according to some 1,300 — before this decomposition takes place, the emanations from one to four days, while in Radium A, B and C the

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changes take place very rapidly — in from three to twenty-eight minutes — but much more slowly — in from six to 143 years — in Radium D, E and F. By means of the electroscope we can measure the gaslike radium emanations and determine their amounts in certain units — Mache units. Besides radium, obtained from pitchblende, we have other radio-active substances which will probably find subsequent therapeutic use such as thorium and actinium.

As to the effects of radium and its decomposition products on the body-tissues, the skin was obviously the first to be studied, and its changes under the influence of radio-active substances are well known, in mild cases we will find redness with swelling and pain, but a return to the normal in about two weeks, in moderate cases, the formation, in addition, of vesicles healing, but with atrophy, in from four to six months, and in severe cases, complete necrosis with ulceration, healing and scar formation being extremely slow.

As regards the effect of radium on other tissues, azoospermia can be produced in animals by exposure to its rays, and also degenerative changes in kidney, spleen, bone-marrow and intestinal follicles, as well as changes, sometimes very grave, in the central nervous system. Bickel and Bergell<sup>1</sup> suggested that the efficacy of many mineral waters might be due to the radium-emanations which they demonstrated in the waters of Wiesbaden and of other spas, this probably explaining the much less marked effects produced by the bottled waters than by those drunk directly from the source, as the emanations are rapidly lost, according to these observers, in forty-eight hours at the longest. They also showed that the radio-active Wiesbaden-Kochbrunnen activates the peptic ferment of the stomach, and thus counteracts the inhibiting effect of the salts themselves, as shown by Schmidt, Pfeiffer, Walberg and others, in the case of certain mineral waters which have lost their radium-emanations by standing. Rodari, however, showed that radium-emanations have no especial influence on the hydrochloric acid of the gastric juice.

In our series of experiments we have studied the influence on pepsin, pancreatic diastase and the autolytic ferment of the liver of the following substances: (1) Radium-Lead powder, (2) radio-active ores shaken up with water and with lead chlorid ( $PbCl_2$ ) in solution in excess, one containing Radium D with a very small amount of Radium E, and being very slightly radio-active, the other, containing Radium D, E and F, being very radio-active, while in our third group of experiments we used Radium D obtained from radium-emanations, 4,800 cc of ordinary tap water impregnated with 50,000 Mache units being evaporated to about

<sup>1</sup> Bickel and Bergell. *Ztschr. f. klin. Med.*, 1905, lxxiii, and *Verhandl. d. Congress f. inn. Med.*, xxi, 157.

250 c.c., radio-activity now being but 0.3 Mache units per c.c., i.e., seventy-five in all

As to the methods employed for the quantitative determination of the pepsin and diastase, but a few words are necessary. For *pepsin*, we used the *edestin* method, putting into each of a row of tubes 2 c.c. of a 0.1 per cent solution, made with hydrochloric acid of the acidity of 30 (decinormal HCl 30 c.c. distilled water 70 c.c.), to each of which row of tubes we had previously added fresh gastric juice (from the dog) in decreasing amounts, 0.5 c.c. in the first, 0.25 c.c. in the second, 0.125 c.c. in the third, etc., bringing up the amount of the fluid in each tube to 1 c.c. with hydrochloric acid of acidity equal to 30, as at this degree of acidity the peptic action seems to be at its optimum. To each of the tubes we then added a certain number of cubic centimeters, three or five of the solution to be tested, to another row of tubes of the same number of cubic centimeters of the control-fluid, distilled water, or evaporated tap water as the case might be, the tubes were tightly corked, kept in the thermostat at 37.5 C. for twenty-four hours, and then tested with a few cubic centimeters of saturated sodium chloride (NaCl) solution, to determine by the white precipitate formed in which tubes *edestin* still remained undigested. The limit of digestion was expressed in units, i.e., the number of cubic centimeters of 0.1 per cent *edestin* solution which would be completely digested by 1 c.c. of pure gastric juice.

The diastase was determined by the Wohlgemuth method, 5 c.c. of a 1 per cent starch solution being placed in each of the row of tubes with pancreatic juice in decreasing amounts, and after the addition of a certain amount of the substance to be tested or of the control-fluid, and 1 c.c. of toluol to each tube to inhibit bacterial action, the tubes were tightly corked kept in the thermostat for twenty-four, forty-eight, seventy-two or ninety-six hours, and then tested with decinormal iodine solution. The digestive power of the juice was again expressed in units, i.e., the number of cubic centimeters of 1 per cent starch solution which would be completely digested by 1 c.c. of pure pancreatic juice. In these experiments the gastric juice was obtained absolutely fresh each time from a dog with a Pawlow stomach, while the pancreatic juice, of which we used two specimens from two dogs, had been obtained a little while before from dogs with operative pancreatic fistulas, and, after the addition of toluol, kept in flasks tightly corked in the ice-chest until needed.

Before describing the method used for the estimation of the splitting produced by the *autolytic ferment* of the *liver*, it might be of interest to say a few words about this ferment.

The numerous activities of that organ, so important in the intermediary metabolism — the liver — are intimately connected with ferments, although we have not found as yet the ferment for every metabolic

process in this organ, nevertheless it is highly probable that it is present. Among the ferments already found in the liver may be mentioned a ferment which splits polypeptides, arginase which acts in the formation of urea, a nuclease, a diastase, a glycolytic ferment, several oxydases, a katalase, a lipase and an enterase. according to Jacoby these ferments are not each in its special type of cell, but the colloid ferment-molecules are in one and the same cell, although definitely separated from each other.

In comparison with the close relationship existing between the liver and the metabolism of the carbohydrates, that between this organ and the proteid metabolism is comparatively loose, although it is *not* probable that the entire protein synthesis has taken place during the passage of the amino-acids through the intestine wall, but probably a part goes through unchanged into the circulation and is synthesized in the liver and other organs. In 1876 Salkowski<sup>2</sup> brought forward the view that the splitting of the protein in the organs during life is caused by intracellular ferments, the purin bases being split off from the nucleoproteins and nucleinic acids.<sup>3</sup> According to Neumeister and Jacoby there is no doubt at present of the constancy of these autolytic appearances dependent on intracellular ferments, probably specific in character. Salkowski<sup>4</sup> found that if fresh liver is finely cut up and chloroform water added to prevent bacterial decomposition, protein digestion takes place in considerable amount. In aseptic autolysis, Magnus-Levy<sup>5</sup> found lactic acid, acetic acid, butyric acid and carbon-dioxid gas. The question whether the autolytic processes are to be regarded as post-mortem phenomena or whether it can be assumed that they play a rôle during life is still under discussion, but the great weight of opinion is in favor of the latter view, i. e., that protein can be broken down in the liver during life into its separate constituents.

The method employed by us to determine quantitatively the extent of this *autolysis* was practically the same as that used by Salkowski and was as follows. Thirty grams of very finely hacked fresh dog's liver was put into a series of flasks, into each of which 50 c c of the fluid to be tested or of the control-fluid with 0.5 c c pure chloroform (or a certain weight of substance, if a solid was used), and then enough freshly and carefully made 1 per cent chloroform-water added to make the total amount of fluid in each flask 300 c c. After being well shaken the flasks were tightly corked, made air-tight with paraffin and placed in the thermostat at 37.5 C. At the end of twenty-four and forty-eight hours, 50 c c of the supernatant fluid was pipetted off from each, the corks replaced and the flasks again made air-tight, while at the end of seventy-two hours in certain experiments ninety-six hours in others, 50 c c of the fluid

2 Salkowski Ber d deutsch chem Gesellsch, 1896, 719

3 Salkowski Ztschr f klin Med, 1891, xii, Suppl p 79

4 Salkowski Festschr f Leyden, 1891

5 Magnus Levy Beitr z chem Phys u Path (Hoffmeister), 1902, ii, 261

was filtered off, as the experiment was then at an end. The 50 cc of fluid was treated as follows. One gram of potassium phosphate ( $K_3PO_4$ ) was added, the fluid was boiled for three minutes and then filtered, and enough distilled water added to the filtrate to bring it up to 50 cc, from 10 cc of this the nitrogen was determined by the Kjeldahl method. If the portions of 50 cc each in the same experiment are put in small flasks of exactly the same size and shape, kept in boiling water in the water-bath for exactly the same length of time (five minutes, for example) and filtered through filter papers and funnels of precisely the same dimensions, it will not be necessary to bring up the last filtrate to 50 cc with distilled water, and a slight source of possible error will be eliminated.

#### EXPERIMENTS

Our experiments were made as follows

##### A With Radium-Lead—

*Autolytic Experiments*—Two control experiments, two experiments with 00465 gr Radium-Lead in each flask, 1 with 0093 gr Radium-Lead twenty-four, forty-eight and ninety-six hours

##### B With Radium D (E) and Radium D, E, F, obtained by shaking up radioactive ores with water, with lead chloride ( $PbCl_2$ ) in excess

1. *Autolytic Experiments*—One control with distilled water (50 cc) one experiment with saturated  $PbCl_2$  solution (50 cc), two with the very slightly radio-active Radium D (E) (50 cc), two with markedly radio-active Radium D, E, F (50 cc), twenty-four, forty-eight and seventy-two hours

2. *Diastase Experiments*—One series of twenty-four hours with 5 cc of distilled water, saturated  $PbCl_2$  solution, Radium D (E) and Radium D, E, F, two series of forty-eight hours, and one of ninety-six hours

3. *Pepsin Experiments*—One series with 5 cc of distilled water, saturated  $PbCl_2$  solution, Radium D (E) and Radium D, E, F, one series—  
 the same without the distilled water control, one series—the same as the first but with 3 cc of fluid in each tube

##### C With Radium D, obtained by evaporating 4,800 cc of ordinary tap water impregnated with 50,000 Mache units of radium emanations to about 250 cc, the radio-activity by this being reduced to 75 Mache units in the entire quantity of fluid, and as control 4,800 cc of ordinary tap water evaporated to about 300 cc (radio-activity=0)

1. *Autolytic Experiments*—Control (50 cc), one experiment with Radium D (50 cc), one control and one experiment using only 12 gm of liver in each flask, 50 cc of control water and Radium D water and chloroform water to 120 cc

2. *Diastase Experiments*—One series of twenty-four hours, two of forty-eight hours, and two of ninety-six hours with 5 cc of Radium D and control-water, one series of forty-eight, one of seventy-two and one of ninety-six hours with 3 cc, one series of twenty-four and one of forty-eight hours, with 5 cc of distilled water, unfiltered control-water and filtered control-water

3. *Pepsin Experiments*—One series with 5 cc of Radium D and of the control-water.

A consideration of the figures and the appended tables will justify us in drawing the following conclusions

In regard to the *autolytic ferment* of the liver, none of the substances used, Radium-Lead, Radium D (E) and Radium D, E, F, from radio-active ores or Radium D from the emanations, had any effect whatever, the figures of the experiments and of the control being practically identical, the higher figures with lead chlorid solution than with distilled water suggest that this salt may have a distinctly activating effect on autolysis, and we hope subsequently to study more thoroughly the influences of this and other salts of the heavy metals on this most interesting type of ferment action.

As regards the *diastatic ferment*, with Radium D (E) and Radium D, E, F from radio-active ores, the former — very slightly radio-active — had practically the same effect as the control — the saturated solution of lead chlorid while the very radio-active Radium D, E, F had a marked inhibiting effect, in all these fluids with lead chlorid in solution in excess, the ferment-action was distinctly inhibited as compared to the action of distilled water. With Radium D obtained from the emanations compared to evaporated tap water (markedly alkaline in this case), each containing considerable sediment and quite a large amount of salts, as in each case 4800 cc of ordinary tap water was evaporated to about 300 cc, most of the experiments showed that the Radium D obtained in this way had a stimulating effect on the diastase, this being more marked the longer the tubes were allowed to remain in the thermostat and the greater the amount of fluid used. A comparison between the evaporated water, rich in salts and sediment, and distilled water showed that the former had a markedly stimulating effect on diastase, this activation being due to the salts in solution and not to the sediment.

As regards *pepsin*, with respect to Radium D (E) and Radium D, E, F each of course, with lead chlorid present in excess, the radium preparations showed a slight inhibiting effect as compared to the saturated lead chlorid solution, this being more marked with the very radio-active Radium D, E, F, a comparison between distilled water and saturated lead chlorid solution showed that the latter had a marked inhibiting effect on pepsin, just the opposite of its effect on autolysis. The results with Radium D obtained from the emanations were inconclusive, due to the lack of material, but the one experiment performed seemed to suggest that the effect was slightly inhibitory.

#### RECAPITULATION

Thus, to recapitulate, none of the radium preparations used seemed to have any effect on the *autolytic ferment* of the liver, although saturated lead chlorid solution appeared to activate it, with diastase the very radio-active Radium D, E, F possessed an inhibiting effect, while the Radium D

from emanations had a stimulating effect, this increasing with the length of time and the amount of fluid used, while this ferment is also markedly activated by the salts in evaporated tap water, with *pepsin* we found a slight inhibiting effect, more marked with the very radio-active Radium D, E, F, although slight in comparison with the inhibiting effect of saturated lead chlorid solution

The detailed figures of the experiments follow

TABLES FOR THE ACTION OF RADIUM AND ITS DECOMPOSITION PRODUCTS ON THE FERMENTS (AUTOLYTIC FERMENT OF LIVER, DIASTASE, PEPSIN)

*A Experiments with the Autolytic Ferment of the Liver*

First Series of Experiments with Radium Lead (Radium-Blei)

	Liver, Chloroform-Water		
	gm	cc	
I	30	300	(Control)
II	30	300	(Control)
III	30	300	00465 gm Radium-Lead
IV	30	300	00465 gm Radium-Lead
V	30	300	0093 gm Radium-Lead

Results (Expressed Both in cc of N/10 NaOH and in Nitrogen)

	After 24 Hours	After 48 Hours	After 96 Hours
I	3 46 cc ( 004858 gm )	6 33 cc ( 008887 gm )	9 03 cc ( 012678 gm )
II	3 25 cc ( 004565 gm )	6 51 cc ( 009140 gm )	8 93 cc ( 012538 gm )
III	3 43 cc ( 004818 gm )	5 83 cc ( 008185 gm )	8 33 cc ( 011696 gm )
IV	3 13 cc ( 004397 gm )	6 7 cc ( 009407 gm )	9 24 cc ( 012973 gm )
V	3 12 cc ( 004380 gm )	6 44 cc ( 009042 gm )	9 2 cc ( 012917 gm )

Second Series of Experiments with Radium D (E) and Radium D, E, F, Obtained from Radio-Active Ores with Lead Chlorid (PbCl<sub>2</sub>) in Solution in Excess

	Liver, Chloroform-Water		
	gm	cc	
I	30	300	(Control)
II	30	250	50 cc sat Pb Cl <sub>2</sub> sol 5 cc CHCl <sub>3</sub>
III	30	250	50 cc Radium D (E) sol 5 cc CHCl <sub>3</sub>
IV	30	250	50 cc Radium D (E) sol 5 cc CHCl <sub>3</sub>
V	30	250	50 cc Radium D, E, F, sol 5 cc CHCl <sub>3</sub>
VI	30	250	50 cc Radium D, E, F, sol 5 cc CHCl <sub>3</sub>

Results (Expressed Both in cc of N/10 NaOH and in Nitrogen)

	After 24 Hours	After 48 Hours	After 72 Hours
I	7 2 cc ( 01008 gm )	8 24 cc ( 01154 gm )	10 82 cc ( 01515 gm )
II	10 7 cc ( 01498 gm )	12 4 cc ( 01736 gm )	15 7 cc ( 02198 gm )
III	11 3 cc ( 01582 gm )	13 9 cc ( 01946 gm )	16 0 cc ( 02240 gm )
IV	11 4 cc ( 01596 gm )	12 9 cc ( 01806 gm )	15 6 cc ( 02184 gm )
V	10 9 cc ( 01526 gm )	12 2 cc ( 01708 gm )	15 7 cc ( 02198 gm )
VI	10 6 cc ( 01484 gm )	12 6 cc ( 01764 gm )	16 4 cc ( 02296 gm )

Third Series of Experiments with Radium D Obtained from Emanations

Control Water 4800 cc of ordinary (tap) water evaporated to (about) 300 cc, radio activity = 0



Radium D Water 4800 cc of ordinary (tap) water with 50,000 Mache units evaporated to 250 cc Radio activity of 1 cc (after evaporation) = 3 Mache unit, i. e., 75 Mache units in the 250 cc.

	Liver gm		Chloroform Water, cc
I . .	12	Control Water 50 cc CHCl <sub>3</sub> 5 cc	70
II.	39	Control Water 50 cc CHCl <sub>3</sub> 5 cc.	250
III . .	12	Radium D Water 50 cc CHCl <sub>3</sub> 5 cc	70
IV. .	30	Radium D Water 50 cc CHCl <sub>3</sub> 5 cc	250

Results (Expressed Both in cc of N/10 NaOH and in Nitrogen)

	After 24 Hours	After 48 Hours	After 72 Hours
I 195 cc ( 00693 gm )			995 cc ( 01393 gm )
II 51 cc ( 00756 gm )		859 cc ( 01203 gm )	108 cc ( 01512 gm )
III 498 cc ( 00697 gm )			1028 cc ( 01439 gm )
IV. 51 cc ( 00714 gm )		79 cc ( 01106 gm )	112 cc ( 01568 gm )

### B Experiments with Diastase

Second Series of Experiments with Radium D (E) and Radium D, E, F, Obtained from Radio Active Ores with Lead Chlorid (Pb Cl<sub>2</sub>) in Solution in Excess

(a)	Substance Used	Diastase in Starch Units		
		In 24 Hours	In 48 Hours	In 96 Hours
	5 cc distilled H <sub>2</sub> O	2560	2560	2560
	5 cc Pb Cl <sub>2</sub> solution (Sat)	1280	1280	1280
	5 cc Radium D (E) water	1280	1280	1280
	5 cc Radium D, E, F, water	320	320	320
(b)	5 cc distilled water		1280	
	5 cc Pb Cl <sub>2</sub> solution (Sat)		640	
	5 cc Radium D (E) water		640	
	5 cc Radium D, E, F, water		80	160

Second Series of Experiments with Radium D Obtained from Emanations (See Under Autolytic Experiments)

(a)	Substance Used	Diastase in Starch Units			
		In 24 Hours	In 48 Hours	In 72 Hours	In 96 Hours
	5 cc shaken, evaporated water	2560	2560	.	2560
	5 cc shaken Radium D water	3840	5120		10240
(b)	5 cc shaken, evaporated water		2560		2560
	5 cc shaken Radium D water		5120		10240
(c)	3 cc shaken evaporated water		1920	1920	2560
	3 cc shaken Radium D water		2560	2560	2560
	3 cc distilled water		640	640	640
(d)	5 cc shaken evaporated water	2560	2560		
	5 cc filtered evaporated water	2560	2560		
	5 cc distilled water	640	640		

### C Experiments with Pepsin

First Series of Experiments with Radium D (E) and Radium D, E, F, Obtained from Radio-Active Ores with Lead Chlorid (Pb Cl<sub>2</sub>) in Solution in Excess

(a)	Substance Used	Pepsin in Edestin Units After 24 Hours in Thermostat
	5 cc distilled water	64,000
	5 cc Pb Cl <sub>2</sub> solution (sat)	12,000
	5 cc Radium D (E) water	8,000
	5 cc Radium D, E, F, water	4,000

	Substance Used	Pepsin in Edestin Units After 24 Hours in Thermostat
(b)		
	5 c c Pb Cl <sub>2</sub> solution (sat )	12,000
	5 c c Radium D (E) water	4,000
	5 c c Radium D, E, F, water	3,000
(c)		
	3 c c distilled water	32,000
	3 c c Pb Cl <sub>2</sub> solution (sat )	12,000
	3 c c Radium D (E) water	8,000
	3 c c Radium D, E, F, water	8,000

Second Series of Experiments with Radium D from Emanations (See Autolytic Experiments)

Substance Used	Pepsin in Edestin Units After 24 Hours in Thermostat
5 c c shaken evaporated water	8,000
5 c c shaken Radium D water	6,000

# PATHOLOGICAL DEVIATIONS IN THE CHEMISTRY OF UREMIC BLOOD \*

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The two theories of uremia that claim most attention at the present time are the toxic and what may be called terminal state—the idea that this condition is not a pathological unity at all but a final dissolution. The latter conception is founded more on the failures of research to elucidate a specific etiological factor than on the lack of a clear-cut clinical picture. Since this idea cannot be tested by investigation, it demands no special consideration. The hypothesis that uremia is a toxic state, however, has much in its favor by way of analogy, and has become more or less rooted in our minds because of the men who have sanctioned this theory in one form or another.

As to the nature of the toxic agent the ideas advanced may be subdivided under two heads, depending on whether the toxic material is supposed to be a normal catabolic product retained in the body through renal failure to eliminate it, or whether this toxic substance is conceived to be the product of a perverted metabolism incident to renal deficiency. The earlier investigators naturally advanced the "retention" theory. Babington, working with a case of uremia under the care of Bright, and Christison, both noted the abnormally high urea content in the blood and attached peculiar significance thereto. Likewise other substances known to occur in urine, creatinin, uric acid, etc., when found in the blood in uremia, were called on to account for the uremic syndrome.

In his conceptions Frerichs departed from the traditional ideas, inasmuch as he believed, not the urea itself, but a substance formed from urea through ferment action, to be the cause of symptoms. This was the first suggestion made that the cause of uremic intoxication depended not on retained excretory substances, but on a product of perverted metabolism. Nearly all of the later investigations on uremia, with the exception possibly of that of Bouchard, have been directed toward the discovery of some product of abnormal metabolism which might account for the nervous manifestations found in uremia. Estimations of "retention" nitrogen and deductions therefrom have been confined in the main to the realm of diagnosis and prognosis.

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Since the toxemic theory of uremia rests at present on no demonstrated facts, it seems desirable to examine the changes found in the blood with a view of ascertaining, in the first place, in how far these deviations from normal are explicable by pure renal failure, and, secondly, any evidence of disordered metabolism

From the chemical point of view, blood plasma may be regarded as a solution of various crystalloids holding in suspension a number of colloids. The latter are various protein, lipoid and carbohydrate substances, while the crystalloids consist of both inorganic and organic substances. Relative to these organic crystalloids it has been repeatedly shown that with some of them at least there is a quantitative increase in the majority of uremic bloods. Qualitative deviations from the normal have been claimed by some investigators, but are not accepted as conclusive for technical reasons. If it were a demonstrated fact, however, that in uremic blood there exists some qualitative change in the content of organic, non-protein compounds, this fact would be of weight in showing an abnormal cellular metabolism. With purely quantitative changes, however, the interpretation would be more difficult. Likewise decided changes in the colloids, or the presence of an abnormal colloidal substance, could hardly be regarded in any light other than fundamentally metabolic. Since any fact that could be demonstrated relative to abnormal proteins might be conclusive, this point was investigated first, although demonstration seems almost impossible in the present state of our knowledge<sup>1</sup>

The chaotic state of knowledge relative to the proteins in blood is dependent primarily on the fact that there is no unanimity of opinion among chemists as to methods. In the first place, sufficient attention has not been accorded to the collection of samples for analysis. Defibrinated blood (plasma), serum and unclotted, centrifugalized blood have been indifferently used, with corresponding discordant results<sup>2</sup>. Even when the same materials have been employed results differed.

That data obtained by using serum expressed from clotted blood can give no idea of actual conditions in circulating blood, has been pointed out by Porges and Spiro<sup>3</sup>. In the separation of globulin from albumin, two methods have been commonly employed: saturation with magnesium sulphate as advised by Hammarsten and Hoffman, and half saturation with ammonium sulphate. As to the relative merits of these two procedures there are two general opinions. Against magnesium sulphate it has been asserted that this salt precipitates not only globulin, but a fraction of the albumin also<sup>4</sup>.

<sup>1</sup> See papers of E. Freud and E. Abderhalden relative to albumose in dog blood. *Biochem. Ztschr.*, 1908, vii, viii, ix, x and xi.

<sup>2</sup> Hoffman. *Arch. f. p. Path. u. Pharm.*, 1883, vi, 183.

<sup>3</sup> Porges and Spiro. *Beitr. z. chem. Physiol. u. Path.*, 1902, iii, 277.

<sup>4</sup> Heynsius. *Arch. f. d. ges. Physiol.*, 1884, xxiv, 330; Marcus. *Ztschr. f. physiol. Chem.*, 1889, xxviii, 559.

On the other hand, objections have been made to the use of ammonium sulphate as a reagent. Wiener contends that other proteins than globulin are thrown down by half saturation unless the serum be much diluted.<sup>5</sup> It appears that if the serum be successively diluted and half saturated with ammonium sulphate, less protein is precipitated than when undiluted serum is used. This difference may amount to 20 per cent. Haslam<sup>6</sup> believes that one-half saturation with ammonium sulphate does not remove all of the globulin from serum, since further saturation effects the precipitation of a protein substance, which on dissolving in water, is precipitated by half saturation. This phenomenon is strongly suggestive of "denaturation." Even less than half saturation of serum with ammonium sulphate is sufficient to precipitate completely all globulins in the opinion of Kander.<sup>7</sup> In view of this disparity of opinion regarding a simple separation it would seem a hopeless undertaking to demonstrate the presence or absence of any protein substance that serum may contain, and in this paper no claim is made for the individuality of such substances. That question has been avoided, to some degree at least, as the results are comparative. Normal bloods were subjected to the same procedures as pathological bloods, and in some cases differences in behavior are recorded.

#### TECHNIC

Since some of the proteins in blood are rendered insoluble in water after contact with alcohol this fact was utilized as the first step in the method, 200 c.c. of citrated blood were thoroughly mixed by shaking with 600 c.c. of alcohol (95 per cent, redistilled with calcium hydrate). After standing for twenty-four hours the alcoholic liquid was filtered off with a suction pump, leaving a granular material in the filter. This precipitate was then suspended in 400 c.c. of distilled water, thoroughly mixed with toluol as a preservative, let stand in a stoppered flask for twenty-four hours, at the end of which time the extract was filtered off and the slightly reddish, translucent filtrate collected. The filtrate contained considerable protein which was in part removed by bringing the liquid to a boil and filtering. This last filtrate was saturated while still warm with ammonium sulphate, which caused a further precipitation of protein like flakes. After standing for twenty-four hours the protein and some excess of ammonium sulphate were removed by filtration<sup>8</sup> and the filtrate freed from the precipitating agent by means of barium carbonate. The final filtrate after this procedure was water-clear and this was evaporated to a small volume (about 25 c.c.) on the water bath.

This method was carried out on two samples of normal human blood, and three samples of blood from uremic patients.

In the case of two of the uremic bloods the final filtrate gave faint but distinct biuret reactions. An endeavor was then made to precipitate any protein still in solution by adding 500 c.c. of absolute alcohol. At first no change was notable but in the course of an hour the material had taken on a milky appearance and by

5 Wiener Ztschr f physiol Chem, 1911, xxxiv, 29

6 Haslam Jour f Physiol, 1904, xxii, 267

7 Kander Arch f exper Path u Pharm, 1886, xx, 411

8 Much more of the excess of ammonium sulphate might have been precipitated with alcohol at this point, and the concentration of liberated ammonia considerably reduced, although it is unlikely that the evolved ammonia had any material effect on the products.

the next day a small amount of white precipitate collected on the bottom of the beaker leaving a clear fluid. This precipitate was filtered off and redissolved in water.

The watery solution gave the following reactions. Potassium mercuric iodid and hydrochloric acid caused a turbidity, as did also phosphotungstic acid and Millon's reagent. Tannic acid gave a small amount of slightly brownish precipitate. The Hopkins-Cole reaction was negative. Trichloroacetic, chromic and phosphomolybdic acids failed to cause change. These reactions were concordant with two samples of uremic blood. With the third sample and with two normal bloods there was no precipitation whatever with absolute alcohol.

An attempt was made with other samples to rid the solutions of ammonium sulphate by dialysis, but it was found that the substance in question was lost in this way. That the substance is readily diffusible was demonstrated on a small portion of the alcohol precipitate. After twenty-four hours' dialysis in a collodion sack, nothing could be recovered.

In addition to the investigation of human bloods, dog blood was studied; one normal and one sample from a dog whose renal arteries had been ligated forty-eight hours before the sample was collected. Both samples failed to yield any protein-like substance after the above treatment.

The results above recorded are not conclusive as to presence of a peculiar protein in uremic blood, and by the methods now known any result could not escape the criticism that the protein substance recovered might have been produced in the process of isolation.

#### NON-COLLOIDAL NITROGEN

The consideration accorded to the non-colloidal nitrogen in uremic blood has been mainly from the clinical aspect, although it should be possible, provided suitable methods are employed, to disclose a deeper significance in the relative distribution of the nitrogen fractions. The method that has been most used in the past for the separation of the blood proteins as a preliminary to determining the "filtrate" nitrogen is that of precipitation by means of alcohol. This method was employed in a preliminary series in order to learn something of the nature of the fractions composing the total alcohol-soluble nitrogen. The technic was to precipitate the proteins of blood by the addition of four volumes of alcohol. Aliquot parts of this filtrate were used for the separate determinations.

The results of analyses recorded in Table 1 require perhaps a word of comment as to their clinical moment. It has been quite positively asserted and with equal conviction denied that the "filtrate" nitrogen is significant, both in diagnosis and prognosis. A glance at Table 1 indicates that, in general, there is a very considerable increase in the amount of

"filtrate" nitrogen in the nephritis patients who are sufficiently sick to seek hospital aid. This, however, is not an invariable rule, and is not to be regarded as pathognomonic, since there are exceptions wherein very severe cases show an approximately normal figure for the "filtrate" nitrogen. Conversely, it has been observed that high "filtrate" nitrogen occurs with other diseases than nephritis, for example, some valvular cases and pneumonia. This does not vitiate all value, but indicates that the results must be interpreted in the light of the whole clinical picture.

TABLE 1.—SHOWING ALCOHOL SOLUBLE NITROGEN AND UREA NITROGEN IN VARIOUS CONDITIONS

Case Number	Date 1910	Diagnosis	Alcohol-Soluble N, g per L	Urea N, g per L	Discharged
20,488	Oct 4	Chronic nephritis	0.00	0.81	
20,488	Oct. 12	Chr nephritis uremia	1.19	0.72	
20,488	Oct 22	Chr nephritis uremia	2.17	1.71	Death Oct 23
20,488	Oct 22	Chr nephritis uremia	1.70		Spinal fluid
20,111		Chr nephritis uremia	3.93	1.10	Death
P. P.	Nov 10	Uremia	3.61	1.72	Death
20,684	Dec 1	Chronic nephritis	1.61	1.10	
20,684	Dec 1	Chro nephritis uremia	2.11	1.78	Death
20,697	Dec 8	Chro nephritis uremia	1.17	0.71	Discharged improved
S. L. H.	1911	Chro nephritis uremia	0.53	0.28	Death
17,521	Jan 20	HgCl. poison	1.15	0.88	Death
17,521	Jan 18	Aneurysm, nephritis	0.52	0.21	Discharged improved
20,650	Jan 18	Chronic nephritis	0.13	0.27	Discharged improved
20,746		Uremia	1.06	0.68	Discharged improved
20,193		Chronic nephritis	1.23	0.66	Death
20,108		Chronic nephritis, cerebral hemorrhage	0.89	0.23	Discharged improved

## KIDNEYS, NORMAL

20,514		Chr valvular disease cerebral embolism	0.12	0.20	
20,511		Gastric ulcer	0.51	0.39	
R. W. C.		Epilepsy	0.33		
R. W. C.		Gas poison	0.76	0.41	
O. P. D.		Gastritis	0.53	0.29	

As to prognosis, the results of analyses in Table 1 at first glance do not appear equivocal. There was, in those cases in which more than one examination was possible, a heaping up of catabolic products as death approached which amounted to an enormous increase over the normal blood content. But that only one analysis gives little information as to the immediate outcome of the case unless the "filtrate" nitrogen is very high, is shown by the results for those cases in which the patient did well notwithstanding the evidence of retention. And one case is of record in

which typical uremia resulted in death although the blood analysis would have indicated an excellent prognosis. When the total alcohol-soluble nitrogen is 1 gm., or over 1 gm. per liter, the prognosis is probably to be regarded as extremely grave, since of eight such cases five terminated fatally. But in order to interpret laboratory results of this nature with accuracy it is necessary to estimate with a greater degree of nicety than we are now able, the efficiency of the heart muscle. It is, in many cases of uremia, by no means easy to determine whether death is due primarily to a toxemia or to a failure of the circulation. There are cases in which the toxic element in the clinical picture is predominant, in others the uremic state is overshadowed by evidences of cardiac incompetence, then the third class in which both factors are detectable, but an evaluation of their relative importance in causing death is most difficult. It is possible that the cardiac element is the explanation of the fatal issue in some of the cases in which "retention" nitrogen is not very much above normal.

The percentage of the alcohol-soluble nitrogen that is found as urea nitrogen is extremely variable and seems to bear no constant relation to the total alcohol-soluble nitrogen. The urea nitrogen may constitute as much as 90 per cent. of this total nitrogen, or be only about 36 per cent. of it. What substances contain the remainder of the nitrogen has been determined only in part. In but a few instances was there sufficient material available for searching analyses. It was found that on evaporation of the alcohol from a portion of the alcohol filtrate the residue has a fatty consistency and it was conjectured that lecithin<sup>9</sup> or some other nitrogenized fat would be detectable. A specimen of uremic blood was examined with this point in view.

An aliquot portion of the alcohol filtrate was evaporated to dryness in a vacuum evaporation apparatus at a temperature of 35 C. A drop of acetic acid was added to prevent the escape of any ammonia during the desiccation. The fatty residue after being mixed with sand was extracted with dry ether in a Soxhlet apparatus for forty-eight hours and the nitrogen content of the ether extract estimated. The results of complete analysis of the serum were as follows:

	Gm. per L.
Total alcohol-soluble nitrogen	0.53
Urea + ammonia nitrogen	0.28
Ammonia nitrogen	0.03
Ether-soluble nitrogen	0.19

The figure for ether-soluble nitrogen is probably too high since even with dry ether it is possible that some urea may go into solution. Also

<sup>9</sup> Letsche. Beiträge zur Kenntniss der organischen Bestandteile des Serums. Ztschr. f. physiol. Chem., 1907, lxxi, 31.



there may be in blood, ether-soluble substances containing nitrogen that are not lipid. In the case of a dog whose ureters had been ligated about the same percentage of ether-soluble nitrogen was found in the blood.

The method of precipitating the protein from blood by alcohol leads to no accurate conception of the relative proportions of the various nitrogenous fractions in the blood, since alcohol may be regarded as a selective solvent in which some substances would not go into solution (e. g., purins, in part), and hence not appear in the filtrate. It is of interest, nevertheless to compare in this connection various samples of blood subjected to this same procedure. The accompanying table (Table 2) shows the results of analyses of uremic blood, compared with analyses of blood in acute renal suppression (sublimite poisoning) and with analyses of the blood of a dog whose renal arteries had been ligated about forty-eight hours before the blood was taken. The quantitative change in the filtrate

TABLE 2.—ALCOHOL SOLUBLE NITROGEN (GRAMS PER LITER)

	Total N	Urea and Ammonia N	Per cent	Ether- Soluble N	Per cent
Human, normal (high)	0.62	0.41	66	0.22	35
Uremia	0.53	0.28	49	0.19	36
Uremia	2.11	1.78	83		
Dog	1.86	1.41	75	0.58	31
Human HgCl. poisoning	1.15	0.88	60		

nitrogen resulting on the suppression of renal activity (mercury poisoning,<sup>10</sup> ligation of renal artery<sup>11</sup>) approaches that found in the severe grades of uremia. In the artificial conditions, however, there are none of the manifestations recognized clinically as uremia.

The question naturally arises at this juncture as to how much the quantitative deviations in the filtrate nitrogen represent purely a suppression of renal function and to what extent they may be interpreted as a morbid metabolic process. In order to gain any insight into this problem another method than that of removal of the blood proteins by alcohol must be employed. The requirements to be met by a suitable process are the removal of all the protein and fatty substances from the

10. Umber. *Chamitc Ann*, 1903, xxvii, 160, v. Jaksch, *Leyden Festschr*, 1902, i, 197.

11. Brown-Sequard. *Arch de physiol*, 1893, v, 777, Ascoli. *Berl klin Wehnschr*, 1902, 561, 634, Soetbeer. *Ges in Giessen*, 1908, xxiii, 6.

blood without affecting the solubility of other substances, in short, a separation of colloids. The method should not be harsh enough to cause the formation of cleavage products from the protein. On this score objection can be made to practically every method that has been employed in the chemical investigations of blood. The absorption methods of Rona<sup>12</sup> are perhaps least open to criticism, because no violent treatment of the blood is necessary, yet all the proteins are completely removed. Whether other substances than proteins are removed also can be determined only by control observations employing varied procedures<sup>13</sup>.

The kaolin adsorption method of Rona and Michaelis was devised to investigate the question of whether sugar exists in the blood in a colloidal state. Theoretically this method will remove from the blood only such substances as are held in colloidal suspension. It is always possible that other materials may be mechanically (or by adsorption) removed as well, but of this little is known. The chief objection in its application to the question under investigation is that hemoglobin is not readily adsorbed by kaolin, which necessitates the use of serum instead of whole blood. This, however, is not a serious deficiency as it is possible to derive purely comparable results. The method employed is to dilute the serum, one part of serum to fifteen or twenty parts of distilled water, five drops of strong acetic acid being added to the diluting water. The proportions in the dilution must be exact to admit of quantitative estimation. To the diluted serum kaolin is now added, 20 gm of kaolin to each 100 cc of the fluid. The kaolin should be introduced in small portions, shaking the mixture repeatedly. After standing for an hour the material is filtered. If the procedure has been properly done a water-clear<sup>14</sup> filtrate results which gives no biuret reaction. The filtrate from normal blood serum treated in this way yields a slight whitish precipitate with phosphotungstic acid reagent, but no effect is produced by Millon's reagent nor by potassium mercuric iodide. There is no precipitate with tannic acid or phosphomolybdic acid. In a number of instances the filtrate was concentrated in a vacuum pan at a temperature of 35 C in order to render

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12 Rona and Michaelis *Biochem Ztschr* 1908 vii, 329, 1909, xvi, 60, Oppler and Rona, *ibid*, 1908, xiii, 121.

13 If blood is a compound, as some investigators, notably of the French school, maintain, wherein all the different ingredients exist in a state of chemical union with each other, then any knowledge of the actual relationship must be out of the question at present.

14 Slight coloring of the serum with hemoglobin does not interfere with the recovery of a protein-free filtrate, but bloody serum can not be employed.

Dr Walter Eddy endeavored to recover proteins from the kaolin mixture left on the filter and found that this could be effected only in part and that the process of recovery changed the proteins to metaproteins.

the above tests more conclusive. There was no change in the reactions in consequence of concentration.

The filtrate from uremic blood is not uniform in all of the reactions secured. There is, as with the normal, a slight precipitation on the addition of pho-photung-tic acid. Both potassium mercuric iodid and Millon's reagent gave precipitates in a few instances, but these reactions were not common to all bloods examined. There was no precipitate caused by tannic acid.

The filtrate was examined after concentration for indol by means of indican, Obermayer's reagent, but it was not detected in any instance.

TABLE 3.—PARTITION OF NON-COLLOIDAL NITROGEN IN SERUM  
SERIES C CHRONIC NEPHRITIS

C <sub>o</sub>	Total Nitrogen, Grams	Urea N, Grams	Per Cent	Purin N, Grams	Per Cent	
19	0.69	0.171	70	0.018	7.3	Uremic coma, died
15	5.37	1.580	35	0.070	1.3	Uremic coma, anuria, died
7	2.16	0.970	45			Large white kidney, uremia, died
12	1.23	0.901	73	0.12	9.7	Chronic nephritis incipient uremia, discharged improved
13	0.96	0.75	78	0.16	10	Second admission in uremic convulsions, discharged improved
20	0.78	0.308	39	0.066	9	Fatty degeneration of kidney, alcoholic wet brain, death
22	0.81	0.38	47	0.143	17	Incipient uremia, discharged improved

SERIES KIDNEYS, NORMAL

16	0.64	0.37	57	0.01	6.5	Gas poison
17	0.68	0.38	56	0.08	11	Gas poison
21	0.46	0.31	71	0.09	20	Gas poison

This is of special interest since Obermayer and Popper found indican peculiarly constant as an ingredient in uremic blood<sup>15</sup>. The subject of indican in blood will be dealt with subsequently.

The quantitative estimations of the various nitrogen fractions in the filtrate were made by the usual methods, total nitrogen by the Kjeldahl method, urea by Benedict's, ammonia by Folin's and purins by the Kruger-Schmidt method. The results of these analyses are shown in

<sup>15</sup> Since it seemed possible that indican might be removed by kaolin, urines were tested by mixing with kaolin and acetic acid. The filtrate gave reactions equally as strong as the untreated urine.

Table 3 The values found for the various nitrogen fractions are in general about the same as those of other investigators, in some cases, however, the absolute quantities are considerably higher, though the percentages are not exceptional<sup>16</sup>

The notable feature in the results of these analyses as in Table 1 is the variability that is indicated in the amount of "filtrate" nitrogen in uremic blood. More than that, not only is the amount of total nitrogen bounded by no definite limits, but also the largest fraction of this total nitrogen, urea, bears no constant relation to the total. In fatal cases the urea nitrogen is 35 to 70 per cent of the total nitrogen while in the less severe cases the extremes are 39 to 78 per cent. There is not in the results here recorded any substantial evidence in support of a possible abeyance of the urea-forming function which might lead to an accumulation of precursors of urea in the blood, since with some small mild cases, at least, the relative amount of urea is as low as with fatal cases. The absolute amount of undetermined nitrogen—which is the fraction of peculiar interest—in some instances (Case 15) suggests a very great concentration, but apparently this appears only when there is a high degree of renal suppression. It is surprising, perhaps, that this is the case, because with a failure to excrete urine the nitrogen substance chiefly affected would be urea, a relatively slight retention of which would increase the

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16 v Jaksch precipitated the proteins with phosphotungstic acid and found from 2 to 3 gm per liter of "filtrate" nitrogen of which 95 per cent was urea. These figures for total "filtrate" nitrogen are too low, since phosphotungstic acid precipitates many non-protein nitrogen compounds, v Jaksch. See Note 10.

Ascoli used sodium chlorid and acetic acid to remove proteins. His values for total nitrogen are 0.94 gm per liter in cases of atrophic kidney, 0.48 gm in parenchymatous nephritis, and 0.99 gm per liter in uremia. *Pflüger's Arch f path Anat*, 1901, lxxvii, 103.

Straus employed heat and acetic acid to coagulate the proteins. He found an average of 0.8 gm per liter in cases of interstitial and 0.39 gm in parenchymatous nephritis. With uremia the "filtrate" nitrogen was increased to over 1 gm per liter. He also noted considerable variations. *Die chronische Nierentzündung in ihre Einwirkung auf die Blutflüssigkeit und deren Behandlung*, Berlin, 1902, p. 68.

Umber precipitated by means of alcohol and fractionated the filtrate with phosphotungstic acid. The average amount of total nitrogen found was about 1.4 gm per liter of which 90 per cent was urea. This very high proportion is the result of the method. *Charité Ann*, 1903, xxvii, 160.

Hohlweg used acetic acid, monopotassium phosphate and half saturation with sodium chlorid to free the blood from protein. In uremia he found considerable variation, between 8 and 30 gm per liter, the latter amount representing the conditions shortly before death. In some cases of nephritis in which the patients died *without uremic symptoms equally high values* were obtained for the *total filtrate nitrogen*. *Deutsch Arch f klin Med*, 1911, civ, 216.

Obermayer and Popper, using heat and acetic acid to coagulate the proteins, found the filtrate nitrogen in uremia between 0.7 and 4.4 gm per liter, of which 21 to 90 per cent is composed of urea. *Ztschr f klin Med*, 1911, lxxii, 333.

The estimations of Widal and his collaborators were made with the hypobromite method which is devoid of accuracy. Personal letter.

blood content considerably, both absolutely and relatively to the total nitrogen. That is to say, with pure retention, as noted in acute renal suppression, the "filtrate" nitrogen of the blood increases rapidly, and all of the factors composing "filtrate" nitrogen increase equally, so that ratios remain fairly constant. Urea nitrogen remains the chief component in the blood as it is in the urine so long as cellular conditions do not change and the percentage of total "filtrate" nitrogen recovered as urea is relatively high. The conditions that might be expected and are found in the blood with pure ablation of renal function are not uniformly fulfilled in the uremic state, although in individual cases they are suggested.

It would be premature to attempt to draw conclusions from data so lacking in accordance as those presented in this paper and it must be left to further investigation now in progress to disclose in uremic blood chemical substances which either quantitatively or qualitatively present a constant divergence from normal.

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# THE EFFECT OF INTRASPINAL INJECTIONS OF RINGER'S SOLUTION IN DIFFERENT AMOUNTS UNDER VARYING PRESSURES

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## INTRODUCTION

This paper is presented as an experimental inquiry into the cause of the severe shock which sometimes follows the injection of serum into the subarachnoid space of the spinal cord. The sole object of this investigation has been to determine the mechanical effect on the spinal and medullary centers, of increasing the amount and pressure of fluid in the spinal subarachnoid space. For this purpose Ringer's solution has been used, as this contains the different inorganic salts of a *real* physiological salt solution, and is therefore preferable to the isotonic solution of sodium chloride commonly called by that name.

No attempt has been made to use serum in any of these experiments, as it was desired to separate the mechanical effect from the obscure symptoms of serum-sickness sometimes produced by injecting a foreign blood-serum. For this reason Ringer's solution was selected, as it contains only the inorganic salts of blood-serum (sodium, calcium and potassium) in the proportion in which they exist in the normal blood.

In order that a post-mortem examination might determine where the fluid had been injected, and the parts to which it had extended during the experiment, an inert coloring matter was added to Ringer's solution. At first lamp black was tried, but proved unsatisfactory, as sedimentation quickly occurred. Liquor carmini was found to answer this purpose, as it is inert and non-diffusible. The carmin is held in solution by glycerin. A mixture of 20 per cent liquor carmini and 80 per cent Ringer's solution was found most satisfactory. In this proportion the amount of glycerin is only present in half the amount used in Toison's fluid, which is isotonic with blood corpuscles and commonly used for blood examinations.

## IMPORTANCE OF SUBJECT AND OBJECT OF PRESENTING IT

Sudden death, with symptoms of collapse, extreme pallor, slow heart and cessation of respiration has been reported in some cases soon after the intraspinal injection of therapeutic agents used to produce spinal

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anesthesia. But it is not probable that spinal anesthesia will ever come into general use. However, since Flexner's discovery of an antimeningococcus serum, this method of medication has become an important one, as it offers the only hope of relief and has reduced the gross mortality from all cases of cerebro-spinal meningitis to about one-fourth of what it formerly was, and in those cases in which the serum had a chance, to approximately one eighth of the former mortality rate.

#### FORMER METHODS

Flexner advised the removal of an amount of cerebrospinal fluid equal to the volume of serum injected, thinking that thereby the intraspinal pressure would not be disturbed and any danger from that source could be avoided in this way. It has been found that this precaution is not

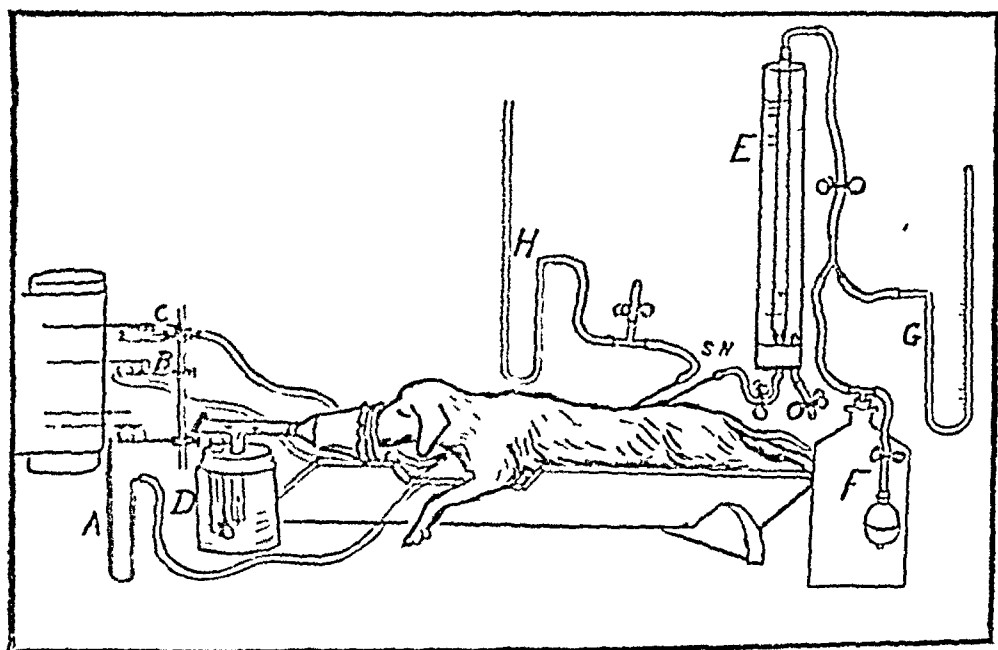


Fig 1—Apparatus used in author's experiments. For explanation see text.

sufficient to prevent sudden death in some cases, either during or soon after the injection.

During the recent epidemic in this state, Dr Abraham Sophian<sup>1</sup> attempted to use the intraspinal pressure as a guide, but found it unreliable and unsatisfactory. Thus if the intraspinal pressure was found abnormally high when lumbar puncture was first made, he allowed the cerebrospinal fluid to escape until the pressure fell to normal (20 to 100 mm of water, or from 2 to 8 mm of mercury). Naturally one would expect that serum could then be injected with safety as long as the pres-

<sup>1</sup> Sophian, A. Jour Am Med Assn, 1912, lvi, 843.

sure did not exceed the original intraspinal pressure Dr Sophian states that the results by this method were misleading and unreliable.

The experiments presented in this paper show that in normal animals there is the greatest variation. In one the respiration will cease when the intraspinal pressure is increased to the equivalent of 10 to 15 mm Hg, in others the intraspinal pressure may be increased above 50 or even 100 mm Hg before alarming symptoms develop. The rapidity with which the pressure is increased seems to be important, but there is some other unknown factor of greater importance, probably the susceptibility of the individual. It may also be that the distribution of fluid injected varies in different animals, accounting for variations in the amount and pressure that may be used with safety in different cases.

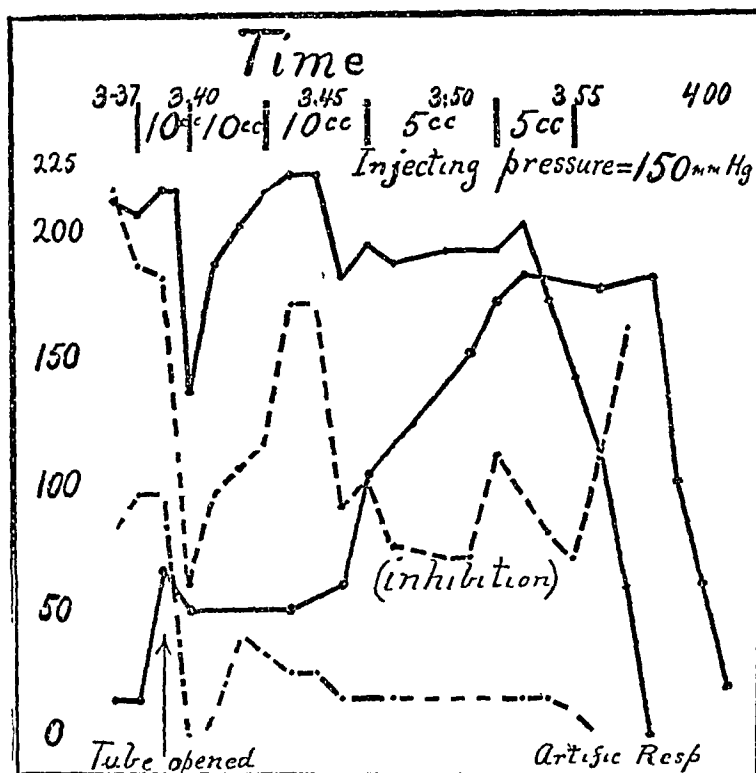


Fig 2 (Experiment 5) — Dog's weight 17.73 kg. Upper continuous black line = blood-pressure, middle broken line = pulse-rate, lower broken line (— — — —) = respiration, continuous line below = intraspinal pressure in mm Hg.

If it is impossible to fix any limit of safety in increasing the intraspinal pressure in normal animals, it is manifestly hopeless to do so in meningitis in which an extensive inflammatory exudate may interfere with the passage of fluid through the spinal into the cerebral subarachnoid space.

Dr Sophian has called attention to the great value of blood-pressure readings as a guide in withdrawing cerebrospinal fluid and in making injections into the spinal subarachnoid space. He states that a fall of blood-pressure equal to 20 mm of mercury is a safe indication to stop.



further injection, that a sudden fall should be a guide not only to the quantity but to the rapidity of injecting the serum. It is obvious that the injecting pressure and rapidity of flow can be controlled better by gravity injections than by using a piston syringe.

These observations are of the utmost importance, for they point out dangers which had not been previously understood and which are not as yet fully appreciated. With a fuller understanding of them we shall probably be able to avoid them. There are a number of reasons why it does not seem practicable for the general practitioner to adopt the method suggested by Dr. Sophian. Many physicians have not had experience in using the sphygmomanometer, and are not familiar with the method of making determinations of the blood-pressure, comparatively few have the special apparatus needed for making these operations, time is of such

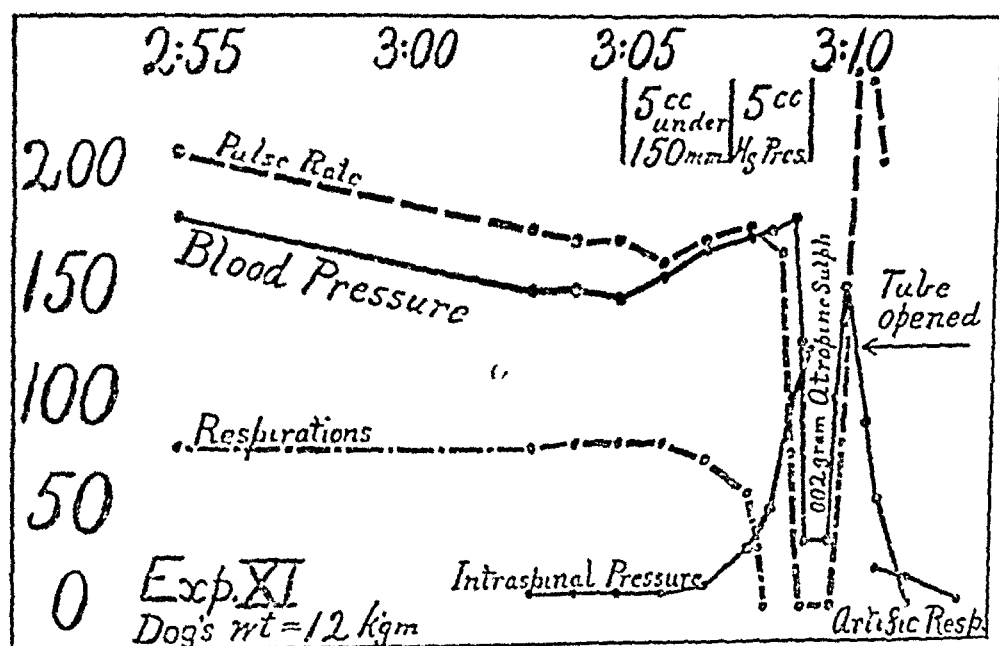


Fig. 3 (Exp. XI) — (curves showing sudden cessation of respiration, followed by complete cardiac inhibition for 30 seconds. Atropin relieved the cardiac inhibition but failed to restore respiration.)

value in instituting proper treatment as soon as the diagnosis is established, that it is not always possible to secure the services of a physician who can take blood-pressure during intraspinal injections, unless it be in a hospital.

Again, the procedure suggested by Dr. Sophian of stopping the injection and giving smaller amounts of the serum at a time seems undesirable. The antimeningococcus serum operates locally by its bacteriolytic action. It seems especially desirable therefore, to give as much as possible, within the limits of safety, in order that it may reach the base of the brain and exert its influence over the entire area involved. It would seem

more desirable to avoid the danger, if possible, than to limit the amount of the injection

What are the mechanical effects of injecting any fluid into the spinal subarachnoid space? How are the alarming symptoms produced? How may they be counteracted, or what is more important, how may they be anticipated and prevented? These are the main questions which we shall endeavor to answer by the experiments presented in this paper

#### PREVIOUS WORK ON THE SUBJECT

Cushing<sup>2</sup> investigated by experiments on dogs the effect of the cerebral compression. This was produced by physiological salt solution introduced under different pressures into the subdural space through trephine holes in the cranium, or into the subdural space in the spinal canal through trephine openings in the lamina of the upper vertebra

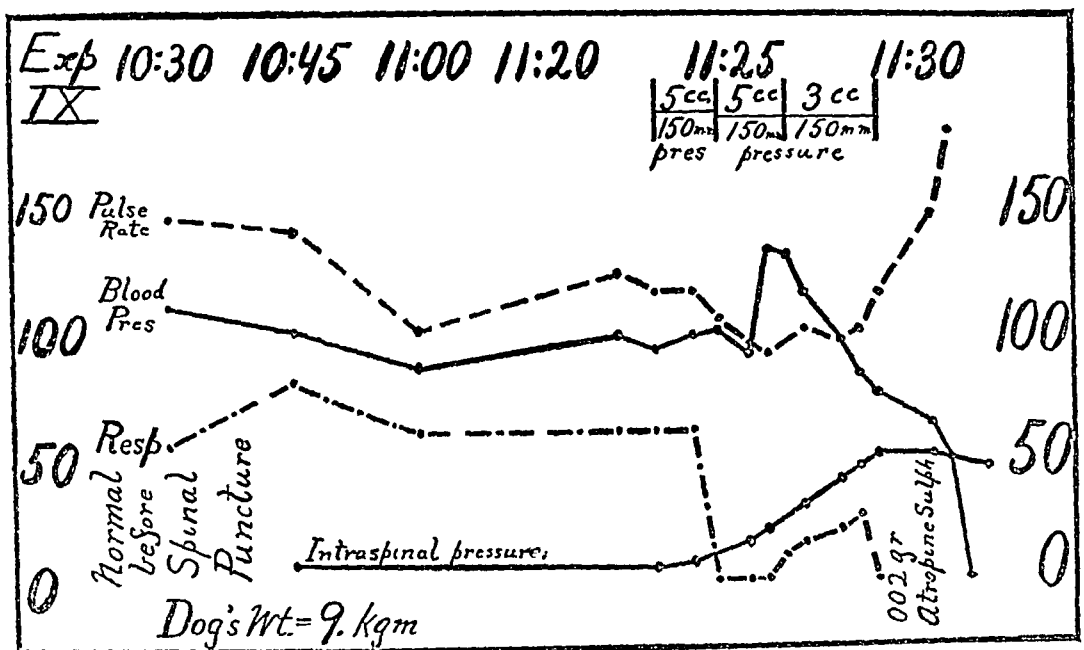


Fig 4 (Exp IX) —Curves of dog with abnormally low blood-pressure. A slight increase of intraspinal pressure caused the respiration to stop without cardiac inhibition. Atropin increased the pulse rate but failed to stimulate the respiratory center.

Cushing found that when the intracranial pressure is increased until it approximates the mean blood-pressure, there is pronounced cardiac inhibition, with very slow, shallow and often irregular respiration, that these effects are most pronounced when the intracranial pressure is increased rapidly and may cause complete cardiac inhibition, lasting from ten to twenty seconds, that this cardiac inhibition can be avoided by section of the vagi

<sup>2</sup> Cushing, H. Bull Johns Hopkins Hospital, 1901, xii, 290

Cushing found that when the intracranial pressure approaches the mean blood-pressure a rise of blood-pressure follows, due to stimulation of the vasomotor center in the medulla. This regulatory action of the dominating vasomotor center is essential in maintaining the capillary circulation in the brain. In this way the blood-pressure may be raised to 200 mm or even 250 mm of mercury or more, and held there until the vasomotor center in the medulla becomes fatigued.

Rehn, quoted by W. C. Lusk,<sup>3</sup> injected physiological salt solution into the spinal cord of animals without recognizable effects. It is probable that he only used small amounts, as he endeavored to find whether the effects of strychnine, novocain and tropacocain were toxic or mechanical, when these drugs are used to produce spinal anesthesia.

#### METHOD OF EXPERIMENTATION

Dogs were used in all experiments. The blood pressure was taken by cannulas introduced into the carotid arteries. One was connected with a mercury

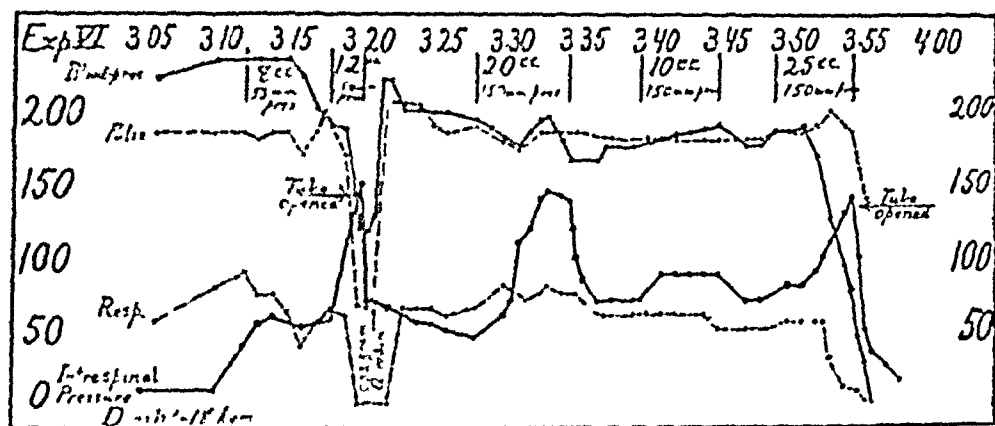


Fig 5 (Exp VI) —Typical experiment of Group II. An increase of intraspinal pressure caused pronounced cardiac inhibition coincident with cessation of respiration. The latter condition persisted for two minutes (one minute after the administration of atropin) but the cardiac inhibition completely disappeared within one half minute after the injection of atropin. Subsequent intraspinal injection failed to produce cardiac inhibition.

manometer (Fig 1, A) while the other was registered by a membrane manometer (B). The latter was used especially to detect any changes in the systolic pressure that might result from alterations in the force of the heart beats, also to show any change in the diastolic pressure in case the vasomotor tone might be disturbed, as in the production of ordinary shock.

A tube introduced into the trachea was connected with a tambour (C) for recording the respirations, and this was arranged to write on the revolving drum on the same vertical line as the writing styles of the two manometers mentioned above. The time was marked in seconds by an electromagnet.

**Anesthesia**—The animals were kept under ether uniformly so that sudden changes in the circulation or respiration could not be attributed to the anesthetic used. For this purpose the inspired air passed through a Mason jar (Fig 1, D)

3 Lusk, W. C. Ann Surg, 1911, liv, 449

mixed with a perfectly uniform ether vapor arising from ether covering the bottom of the jar. Light respiratory valves of aluminum disks caused the exhaled air to escape without passing through the jar. The arrows in Fig. 1 show the direction of the currents of inspired and expired air. In this way there was no variation in the vapor density at any time, as the minimum amount of ether for maintaining light anesthesia was used.

This method of maintaining uniform anesthesia for long experiments has been used successfully in the laboratory for the past two years and eliminates from consideration any possibility of a complication from the anesthetic which could account for the profound disturbance of the respiration and circulation that results from intraspinal injections

*Mode of Injection*—The carmin-Ringer's solution was injected from a graduated buret so that small amounts could be measured accurately. The buret (Fig 1, E) was connected with a needle used for spinal puncture by a short length of rubber tubing with a spring pinch-cock. A large glass tube, like that used for condensers, surrounded the buret. This was filled with luke warm water constantly so that the fluid entered the spinal canal at the bodily temperature.

The injecting pressure, under which fluid was forced into the spinal canal, was exerted by compressed air. The bulb of an atomizer was attached to a T-tube in the stopper of a half-gallon bottle (Fig 1, F), a piece of rubber tubing connected the bottle with the top of the buret; interposed between the two another T-tube connected with a mercury manometer (G) so that the pressure of the

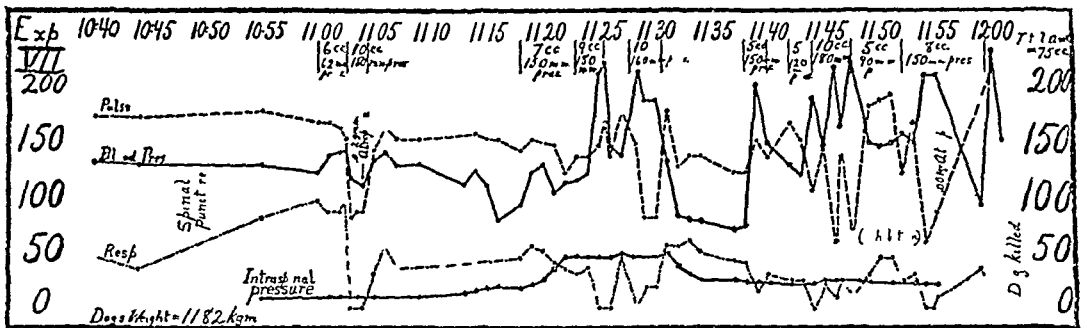


Fig 6 (Exp VII) —Another experiment of Group II illustrating the points mentioned under Fig 5 The intraspinal injections made after the administration of atropin caused serious disturbance of respiration without dangerous cardiac inhibition The blood-pressure rose from the late injections

compressed air was measured accurately in mm Hg, and could be kept uniform within variations of 5 mm

*Spinal Punctures*—These were made by needles used for giving serum in man. The lower one was introduced between the lumbar vertebrae at the level of the top of the pelvis, the second spinal needle was introduced one or two spaces above the first (Fig 1, S N)

The injection was usually made through the lower needle, while the intraspinal pressure was usually taken by the upper one. The latter connected by means of rubber tubing with a mercury manometer (Fig 1, H) with a T-tube interposed between the two. The side arm of the T enabled all air to be replaced by Ringer's solution, it also afforded a means of allowing fluid to escape quickly from the spinal canal, thereby lowering the intraspinal pressure.

Difficulty was experienced in getting needles of suitable size for spinal puncture in dogs. The smaller ones are easily occluded and offer great resistance to the flow of fluid through them, the larger ones are difficult to introduce between the vertebrae and often the beveled end punctures the spinal membranes without conveying all of the fluid into the subarachnoid space.

Spinal fluid escaped from the first needle introduced but often it was impossible to get any from the second one probably on account of the small amount and low pressure in the normal animal. Frequently the upper needle touched the spinal cord but the blood pressure was taken before and after the puncture. If any shock followed the introduction of the needles, time was allowed for this to pass off before starting the injections.

The intraspinal pressure was noted by one observer and called to another who recorded it immediately under the registration of the blood pressure on the revolving drum. In some of the experiments the intraspinal pressure was recorded on the drum by a writing style on a mercury manometer, as Cushing made a tracing of the intracranial pressure.

*Autopsy.*—Immediately after each experiment an autopsy was made to determine if both needles had punctured the membranes, the location of the fluid injected, and the extent to which it had extended to the intracranial cavity.

The brain and cord were removed and fixed in 10 per cent dilution of liquor formaldehyde in distilled water. The alkaline salts of tap water cause the solution and diffusion of some of the curium injected.

#### RESULTS OF EXPERIMENTS

The first experiment was made with only one needle introduced into the spinal subarachnoid space. The intraspinal pressure was measured

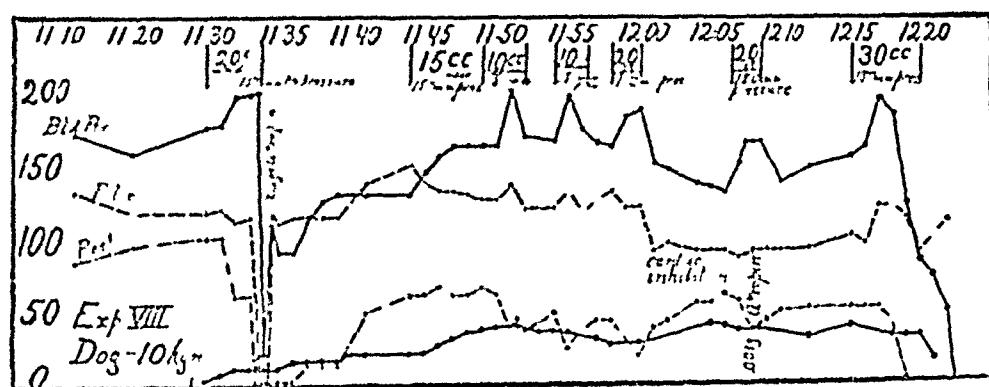


Fig. 7 (Exp. VIII) — Another experiment of Group II. A slight increase of intra-spinal pressure to 10 mm Hg caused sudden cessation of respiration followed by abrupt and complete cardiac inhibition. Atropin restored the normal heart beat within 10 seconds but spontaneous respirations only started after three minutes of artificial respiration.

Subsequent to the administration of atropin, the intraspinal injection of a larger amount of Ringer's solution, under a higher injecting pressure, failed to produce cardiac inhibition, but each injection reduced the respiratory rate greatly. The blood pressure rose in these late injections as in Experiment 7 (Fig. 6).

before the injections, and again after they had been completed, but there was no increase over the normal (15 mm Ringer's solution or 3 mm of mercury).

Injections of 3 to 1 cc were made at a time, taking from two minutes to thirty seconds for each injection as the injecting pressure increased. Starting with an injecting pressure of 30 mm of mercury, it was increased to 50, 80, 100, 120, 140, 160, 200, 230 and 250 mm of mercury at succeeding injections.

A total of 29 cc was injected in a dog weighing 17.73 kilograms in the course of thirty minutes, with practically no effect until the injecting pressure had been increased above 100 mm of mercury. With an injecting pressure between 120 mm and 250 mm of mercury, there was a moderate decrease of the respiratory rate, a slight increase of blood-pressure, with a decrease in the pulse-rate. The change was not more than one-tenth of the normal in any one, and the symptoms were not serious at any time. The animal was killed by chloroform. This experiment was remarkable for the slight disturbance produced by an enormous injecting pressure. The distribution of the pigment at the base of the brain and on the cortex showed that the fluid injected had reached the cerebral subarachnoid space but evidently the pressure of fluid within that space had not been materially increased.

The intraspinal pressure was measured throughout the other experiments, but it was found that there is a wide variation in the extent to which it may be increased before alarming symptoms develop. In most instances a *rapid increase* in this pressure was the most important danger

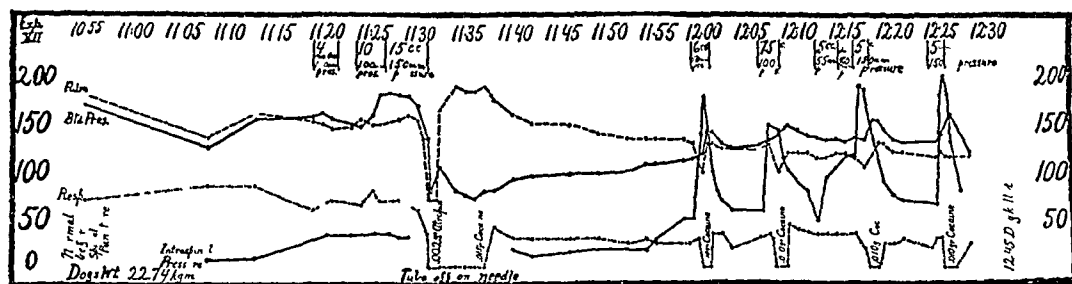


Fig 8 (Exp XII) —Experiment illustrating Group III. Atropin removed the cardiac inhibition immediately but failed to restore respiration. Although artificial respiration was kept up for five minutes, there was no attempt at spontaneous respiration. The injection of 0.010 gm cocaine started natural respiration at once.

Four injections after the administration of atropin caused cessation of respiration without cardiac inhibition, after waiting one minute for spontaneous respirations each time, the injection of cocaine restored natural respiration promptly.

signal, but this was not constant, and no limit of safety can be fixed either as to the amount of fluid that may be injected, or the degree to which the intraspinal pressure may be increased.

In some experiments the most serious disturbance of the respiration and circulation occurred, with apparently very little or no increase of the intraspinal pressure. In these it is probable that the opening of the needle was occluded by membranes or by a clot, so that the actual intraspinal pressure was not registered by the manometer. Experiments 6 and 8 illustrate this point. Every effort was made to clear the needle when this condition seemed probable, but it is impossible to be certain that this is patulous when variations of pressure do not occur. In some experiments

no variations of intraspinal pressure could be obtained, and the injections were continued until characteristic symptoms developed

In some experiments large amounts of fluid were injected with comparatively little increase of the intraspinal pressure. It is probable that this was due to some escape of the fluid to the extradural space, as it was often necessary to make a number of punctures in attempts to get the needles in the proper place. This condition obtained in the experiments of Group V.

In a few instances the intraspinal pressure rose rapidly, usually toward the end of the injection or immediately after it, and exceeded the injecting pressure recorded. This apparent discrepancy is explained by the fact that only the pressure of the compressed air was recorded as the injecting pressure. The column of fluid in the buret was not considered, as it was subject to variation. When the buret was filled it added a column of Ringer's solution 530 mm in height, or a pressure of 40 mm of mercury to that recorded as the injecting pressure. With the arrange-

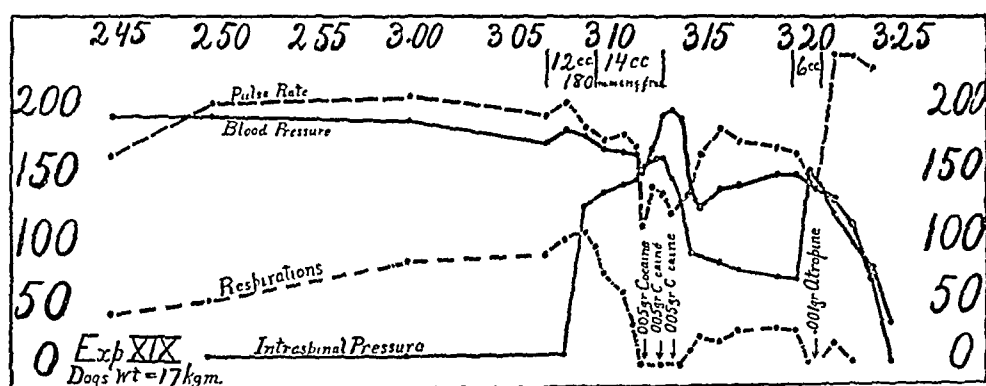


Fig 3 (Exp XIX) —This is one of eight experiments of Group IV, in which the cardiac inhibition was a less serious consequence of the intraspinal injection than the complete cessation of respiration.

The injection of cocaine restored natural respiration promptly, but this drug had practically no effect upon the cardiac inhibition. When subsequent intraspinal injections produced characteristic symptoms, atropin failed to restore respiration but caused cardiac inhibition to disappear promptly.

ment for keeping the fluid at body temperature, and for measuring the amount injected each time, it was impossible to overcome this difficulty.

Sudden variations of intraspinal pressure may occur during and immediately after intraspinal injections. Probably these are due to the distribution of the fluid injected in the subarachnoid or subdural space, variations of the intracranial pressure, or the blood in the plexus of the veins in the extradural space of the vertebral canal.

The experiments may be divided into five groups, and the diagrams on which the changes have been plotted show typical results better than a detailed description.

In the diagrams the time is given at the top The time of each injection is marked by vertical lines, the amount injected and the injecting pressure are indicated between these vertical lines

The numbers at the sides show the blood-pressure and intraspinal pressure in millimeters of mercury, also the pulse-rate and respiratory-rate per minute The upper continuous line represents the blood-pressure, the upper broken line, the pulse-rate, the lower continuous line represents the intraspinal pressure, the lower broken line (— —) shows the number of respirations per minute

GROUP I—Experiments 5, 9 and 11 (Figs 2, 3 and 4) were of brief duration The injections caused death in a very short time from cessation of the respiration and pronounced cardiac inhibition The respiration ceased from one to three minutes before the heart stopped, and in two of these experiments death occurred in spite of artificial respiration

Lowering the intraspinal pressure relieved the cardiac inhibition temporarily in Experiment 5, but failed to do any good in Experiment 9

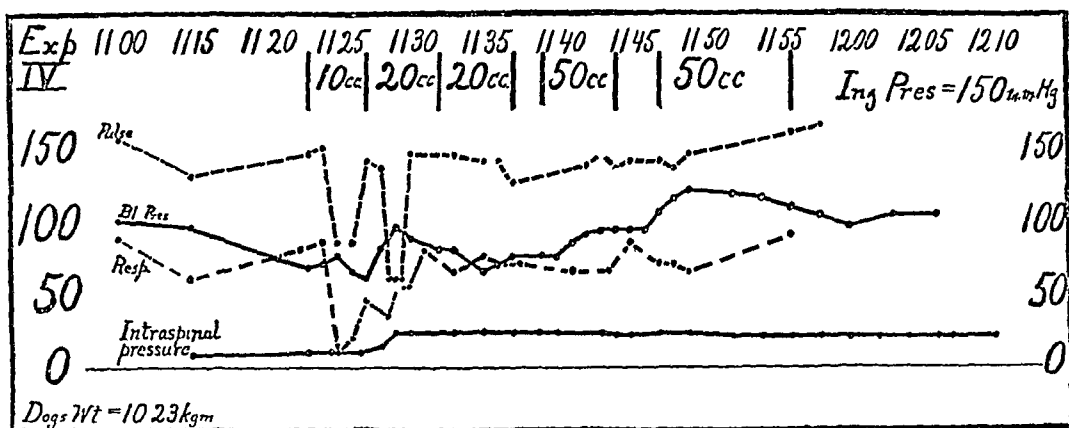


Fig 10 (Exp IV) —As a type of Group V The first two injections produced some cardiac inhibition but subsequent injections of larger amounts had no effect These exceptional results are explained by the escape of the fluid to the extradural space as described in the text

The administration of atropin after alarming symptoms had developed (Exps 9 and 11) caused the cardiac inhibition to disappear but failed to start the respirations, and the animals soon died

In the experiments of this group comparatively small amounts of fluid were injected, viz, 10 cc, 13 cc and 40 cc. The injecting pressure (from compressed air) was 150 mm of mercury, plus the column of fluid in the buret The latter varied from the equivalent of 10 to 40 mm of mercury, as previously explained

Serious symptoms developed when the intraspinal pressure had been increased to 7 mm, 26 mm and 66 mm of mercury in the respective experiments Fatal results occurred when the intraspinal pressure had been increased to 50 mm, 116 mm and 180 mm Hg.



The fall of blood-pressure was due entirely to the profound cardiac inhibition, probably from stimulation of the centers in the medulla. There was no loss of vasomotor tone as in surgical shock. The diastolic pressure recorded by the membrane manometer showed no change except that which occurs with cardiac inhibition. As soon as the latter disappeared from the administration of atropin, the systolic, diastolic and mean blood-pressure returned to normal. No attempt has been made to plot the systolic and diastolic pressure on the diagrams, as they show no change.

Two of the experiments of this group show unusually high blood-pressure (Exps 5 and 11). In both instances the respiration ceased before the blood-pressure had been reduced to an abnormally low level by the pronounced cardiac inhibition.

This is of interest, for it shows that an abnormally high blood-pressure, such as occurs from increased intracranial pressure, is not sufficient to prevent the mechanical effects of intraspinal injections on the centers of the medulla. Robinson<sup>4</sup> found that the blood-pressure was increased in a considerable proportion of the twenty-six cases of cerebrospinal meningitis patients studied by him, while it was decreased below the normal in others.

In Experiment 9 the blood-pressure was unusually low, as the animal was suffering from distemper. In this case the paralysis of the respiratory center was the most serious disturbance, while the cardiac inhibition was less conspicuous.

GROUP II.—In this group (Experiments 6, 7 and 8, Figs 5, 6 and 7) pronounced cardiac inhibition, preceded by a cessation of respiration, occurred early in the experiment, after the injection of a comparatively small amount of fluid (6 to 20 cc). The administration of atropin promptly restored the circulation to normal and respiration was then reestablished.

A much larger amount of fluid (30 to 100 cc) was subsequently injected by repeated injections, some of them made under higher injecting pressure, without producing cardiac inhibition or serious fall of blood-pressure. The respiration ceased a number of times from the later injections, but it was not so easily affected in the absence of circulatory disturbances.

These experiments show that atropin prevents the effect of intraspinal injections on the heart but not on the respiration, also that the fall of pressure is not due to loss of vasomotor tone from depression of the vasomotor centers, but to cardiac inhibition.

Experiment 7 is of particular interest in this connection. The first injection had the usual effect. After atropin had been administered the subsequent injections caused a rise of blood-pressure, going above 200 mm of mercury repeatedly, the elevation of pressure being proportionate to the

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4 Robinson THE ARCHIVES INT MED, 1910, v, 482

injecting pressure used This must have been due to the stimulation of the vasomotor center in the medulla, as explained by Cushing This experiment shows that intraspinal injections made by lumbar puncture may have the same effect that Cushing obtained by increasing the intracranial pressure, if cardiac inhibition is prevented In spite of the rise of blood-pressure, the respiration ceased after each injection

GROUP III —Experiment 12 (Fig 8) of this group differs from those of the preceding group, in that atropin did not restore the blood-pressure so promptly, although it immediately removed the cardiac inhibition In this experiment there was decreased vasomotor tone, as shown by the low diastolic pressure Natural respiration did not return after artificial respiration had been kept up for five minutes The intravenous injection of cocain reestablished respiration at once

Subsequent injections caused the respiration to cease without any material change of blood-pressure or pulse-rate After waiting one-half to one minute, without artificial respiration or any sign of recovery, the injection of 0.010 gm of cocain caused the normal respiratory rate to return In this condition, as in ether narcosis, cocain is a valuable respiratory stimulant

GROUP IV —This group includes eight experiments, of which Experiment 19 (Fig 9) shows typical results

Characteristic symptoms (cessation of respiration and cardiac inhibition) followed the intraspinal injection, but the cardiac inhibition was less pronounced Cocain was given alone, or it was given first and atropin was administered a considerable time later

In each case cocain promptly restored the respiration, but failed to remove the cardiac inhibition In some instances the cardiac inhibition was not lessened at all by the cocain, in others the cardiac inhibition gradually disappeared with the reestablishment of respiration to normal The subsequent injection of atropin caused the immediate and complete disappearance of the cardiac inhibition

This indicates that the cardiac inhibition is due to direct stimulation of the cardio-inhibitory center in the medulla, and does not result as one of the symptoms of asphyxia following the paralysis of respiration

It is also obvious that both atropin and cocain are required to meet the disturbances of the circulation and respiration Neither of them acting alone can meet the indications It is also apparent that there is not sufficient time for using these drugs after alarming symptoms develop from intraspinal injections in man In the experiments presented in this paper the injections were made directly into the jugular vein, but even then the result was uncertain

The condition is analogous to the collapse which sometimes develops in chloroform narcosis from sudden stoppage of the heart due to cardiac

inhibition It can easily be prevented by the preliminary administration of atropin, while all efforts at resuscitation often fail after a concentrated vapor of chloroform has produced the condition

GROUP V —Experiments 3, 4, 10, 13, 18, 22 and 25 (See Fig 10 for Experiment 4) are remarkable for the large amount of fluid injected without the production of any symptoms or only mild and transitory disturbances In these experiments the amount injected varied from 60 to 150 cc, but the intraspinal pressure was low as a rule (See curves of Experiment 4)

The autopsy in each case showed a large amount of the carmin-Ringer's solution in the extradural space of the spinal canal There was no pigment at the base of the brain or on the cortex and very little beneath the spinal arachnoid Even the lining of the dura shows comparatively little pigmentation, so that most of the fluid must have been injected into the extradural space and doubtless escaped through the intervertebral foramina

The failure to obtain any change in the circulation or respiration can easily be explained by the post-mortem finding, for an examination of the brains of these dogs shows that practically none of the fluid entered the cranial cavity and very little passed up the cord

#### INCIDENTAL OBSERVATIONS

The question as to the distance to which fluid (e g, serum) reaches when given by lumbar puncture can be definitely answered by the autopsy findings of the first four groups of experiments and by other preliminary experiments Even small amounts under low pressure reach to the base and cortex of the brain

Small amounts under moderate pressure probably do not reach into the lateral ventricles At least carmin has only been found in those experiments in which a large amount of fluid had been injected under high pressure Under these circumstances the lining of the ventricles is pigmented distinctly It is doubtful if serum injected under the pressure which would be safe to use in man, ever reaches the lateral ventricles

#### CONCLUSIONS

1 No definite limit can be fixed to which the intraspinal pressure may be increased with safety In some animals serious symptoms developed when it was increased to 10 mm of mercury, while in others this only occurred with a pressure of 50 or 60 mm of mercury

2 The normal intraspinal pressure in dogs varies from 3 to 10 mm of mercury or 40 to 135 mm of water A sudden increase of pressure, even though a small amount be given is more dangerous than a larger amount given gradually by gravity

3 The first mechanical effect of increasing the intraspinal pressure from injections made by lumbar puncture is the cessation of respiration, quickly following it, or coincidently with it, there is profound cardiac inhibition, which causes a tremendous and sudden fall of blood-pressure. The fall of pressure is often so abrupt that it frequently drops from normal to zero within a half minute.

4 Atropin removes the cardiac inhibition and restores blood-pressure by its paralyzant effect on the cardio-inhibitory nerve center.

5 Atropin fails to stimulate the respiratory center, while cocain is the most valuable respiratory stimulant for such an emergency.

6 These drugs should be given together in full doses before making a spinal puncture or intraspinal injection. The injection at the site of spinal puncture would also produce local anesthesia. The condition could thus be prevented more easily than it can be remedied after alarming symptoms suddenly develop. This is particularly true if chloroform is used as an anesthetic, as the inhalation of chloroform in concentrated vapor produces similar effects and thus makes the condition more serious.

7 The fall of pressure is not due to a vasomotor disturbance. There is, therefore, no indication for the administration of epinephrin. On the contrary, it is positively contra-indicated on account of its well-known action in producing cardiac inhibition.

8 Lowering the intraspinal pressure by allowing fluid to escape from the needle after the characteristic symptoms develop, fails to relieve the condition.

9 The advantage of using atropin and cocain before intraspinal injections consists not only of lessening the dangers of sudden death, but it enables a *larger amount* of fluid to be injected without producing dangerous symptoms from the mechanical effect. This is a great advantage in administering antimeningococcus serum, as its action is chiefly a direct, local one on the living bacteria and the benefits are in proportion to the amount administered.

# TWO CASES OF ANAPHYLACTIC SERUM DISEASE OVER SIX YEARS AFTER THE PRIMARY INJECTION OF HORSE-SERUM (YERSIN'S ANTI-PEST SERUM)

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The widespread interest in hypersusceptibility and allergy and their relation to infectious disease leads me to report two cases of this nature following over six years after the primary injection of horse-serum

I desire also to express the personal feeling that the use of diphtheria antitoxin for the immunization of *contacts* (the immunizing dose) should be avoided as often as practicable. I believe it is much wiser and shows more consideration for the patient for contacts to be examined from day to day and for cultures from the throat to be examined as well. In this way the disagreeable features of serum disease and the indiscriminate and widespread sensitization of many persons to horse-serum will be avoided.

Serum disease is a term used by von Pirquet and Schick<sup>1</sup> to denote the clinical manifestations following the injection of horse-serum. These symptoms may follow the primary, secondary, or other subsequent injection of serum. The first injection of horse-serum often causes symptoms peculiar to the serum itself, such as urticaria, fever, edema and joint pains. These are not due to the antitoxin, but to the horse-serum, and they only occasionally occur immediately after the injection. There is nearly always a latent or incubation period of eight to twelve days. Von Pirquet has noted that following the second injection of horse-serum, the reaction is altered as to time, quantity and quality, and these altered manifestations he has termed allergy (altered reaction).

With regard to the incidence of serum disease, Weaver<sup>2</sup> records that 31.1 per cent of 692 patients with diphtheria to whom serum was administered, observed for ten days or more, exhibited the reaction.

The amount of serum injected to a great extent determines the appearance of the reaction. Thus, Weaver notes that when 1 to 9 c c of serum was administered, 10.9 per cent of patients, observed for ten days or more, showed a reaction. When 100 to 109 c c were given, 44.4

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\*Read at Meeting of Canal Zone Medical Association, May 8, 1912

1 Von Pirquet and Schick. *Leipsic, Denticke, 1905*

2 Weaver, G. H. Serum Disease, *THE ARCHIVES INT. MED.*, 1909, III, 485

per cent of patients showed a reaction, while in eight patients, given 170 to 280 c c of serum, all, or 100 per cent, showed a reaction

*Serum disease following a primary injection of horse-serum* This appears after an interval between the injection and the appearance of symptoms At the end of the period of incubation, the symptoms suddenly appear Locally, there is redness and itching of the skin The general symptoms are fever, edema, skin eruptions, such as urticaria and erythema, swelling of lymph-nodes, leukopenia, joint pains, occasionally nausea and vomiting, there is some headache, backache and soreness and aching of the muscles, and in severe cases prostration and a tendency to fainting

*Serum disease following a secondary injection (toxic injection) given after a considerable interval (Anaphylaxis)* Ten days or more after a primary injection the exhibition of a second injection elicits symptoms of serum disease, either immediately or after a period of incubation shorter than that following a primary injection (allergy) The "immediate" reaction occurs within a day, while the "accelerated" reaction occurs usually within five to seven days after the secondary injection The local symptoms are specific edema and urticaria at the site of inoculation The general symptoms are fever, chilliness, exanthematous eruptions, urticaria, edema and joint pains, and in severe cases there is prostration and a tendency to fainting

Von Pirquet<sup>3</sup> states that after the first injection of horse-serum, serum disease appears seldom before the sixth day, oftenest on the eighth or ninth day, but frequently later When individuals receive a secondary injection, the symptoms usually appear as an immediate reaction within twenty-four hours, and he noted that in children receiving a second injection, a number reacted on the sixth and seventh days This von Pirquet and Schick called the "accelerated" reaction

The secondary injection must be many times larger in amount than the minimum "sensitizing" injection in order to elicit visible symptoms, so that on this account it would seem to be impossible to determine by means of a cutaneous reaction whether an individual were sensitive to horse-serum

Von Pirquet explains the phenomena of anaphylaxis or allergy as follows In serum disease, for example, horse-serum is injected into man, and antibody is formed We see at this time that symptoms of disease appear and the supposed connection is that the symptoms are due to toxic bodies formed by the digestion of the antigen (allergen) through antibody On a second injection ("toxic dose") it is assumed (a) that the antibody is already present and when the horse-serum is injected the

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3 Von Pirquet THE ARCHIVES INT MED, 1911, vii, 259 and 383

toxic bodies are now formed and elicit an immediate reaction. It is assumed (b) if the second injection follows long after the primary injection the blood is free from antibody as well as horse-serum, but the body cells, however, having once made them, now make antibodies rapidly, so that in this case antibodies are formed more or less quickly. The toxic bodies are then formed and elicit the symptoms in an "accelerated" reaction.

In severe cases of serum disease there is more or less prostration and cardiovascular weakness. These symptoms are no doubt analogous to those elicited in experimental animals on the administration of secondary toxic doses of horse serum to sensitized subjects, and Auer<sup>4</sup> has called attention to the interesting fact that symptoms and signs of anaphylaxis differ considerably in three species of animals which have so far been carefully studied. The characteristic drop in blood-pressure of dogs shown graphically so well by Pearce and Eisenbrey,<sup>5</sup> is not found in the acute cases of anaphylaxis in the rabbit and guinea-pig. The large, pale, inflated lungs in the guinea-pig are not found in the dog or rabbit, and, again, the intravital rigor of the heart muscle in the rabbit is not seen in the dog or guinea-pig. In the rabbit Auer demonstrated that the heart itself is the vital cause of death in acute anaphylaxis in rabbits.

#### CASE REPORTS

Among the personnel at Ancon Hospital in May, 1905, S T D, who performed the autopsy, and H W, an attendant, were exposed to a case of bubonic plague and each received 10 c c of Yersin's antipest serum. The same individuals, in October 1911, were similarly exposed to a case of septicemic plague, and again received 10 c c of Yersin's antipest serum. At this time fifteen other individuals who had been exposed received injections of the serum. Among these was H C C, and of the seventeen persons injected, S T D, H W and H C C developed serum disease, while none of the fourteen who had not been previously sensitized by horse-serum developed any symptoms of serum disease.

CASE 1—S T D, physician, aged 39, had never had diphtheria, nor received injections of horse serum. He performed an autopsy on a case of bubonic plague June 23, 1905, and on this date received the equivalent of 10 c c of Yersin's antipest serum. This was a dried horse serum taken up with saline solution. No symptoms of serum disease followed the injection.

Oct 17, 1911, nearly six years and four months later, he performed an autopsy on a case of septicemic plague and the following morning received 10 c c of Yersin's antipest serum (liquid horse serum). Following the injection there was some redness at the point of inoculation, but no other signs until October 23 (sixth day), when the skin area corresponding with the location of the injection

4 Auer *Jour Exper Med*, 1911, xiv, 493

5 Pearce and Eisenbrey *Jour Inf Dis*, 1908 vii, 573

itched intensely and an urticarial rash 6 to 7 cm in diameter appeared there. The following morning (seventh day) the urticaria spread to the groins, inner aspects of thighs and the scalp. By noon almost all parts of the body above the knees were involved. While the pain and discomfort were severe, there were no other symptoms until 1 30 p m, when he was awakened from a siesta by a feeling of intense depression as though fainting. The pulse could not be detected at the wrist. Yawning or sighing was frequent. A few minutes later the pulse was found to be 46, the features ashy-white, there was cold perspiration and an intense feeling of prostration. During the afternoon periods of intense stinging or tingling of the skin with tremendous edema of the scalp, lips, forehead and body were followed by attacks of prostration and feeble pulse. Each period lasted about fifteen minutes. There were also small circumscribed patches of pain in the epigastrium, esophagus (?) and right chest below the right nipple. On swallowing a glass of water on one occasion, it appeared that there was some swelling of the mucosa of the esophagus, for there appeared to be some resistance to the passage of fluid. During the afternoon attempts at rising and walking a few steps were quickly followed by fainting sensations and hallucinations of vision. Stychnin sulphate 1/30 gr was administered hypodermatically in the left arm and the arm remained very tender and sore for two days. The intense itching kept up during the night but there was no distress or prostration. On October 25 there was some urticaria of the legs, particularly the soles of the feet. The patient could not sit up without discomfort. Large urticarial wheals appeared on the neck in the afternoon and there was some general neuralgia-like pain.

October 26. During the night there were large patches of urticaria on the knees and during the day backache and neuralgic pains all over the body. It appeared to the patient that the spells of depression or prostration were to some extent averted if the desire to scratch the areas of urticaria were controlled.

October 27 to 30. Patient felt weak, the muscles were sore and he had a haggard look. November 1. General feeling of well-being returned. November 2. A papular rash that itched or tingled slightly appeared on the breast and sides of chest from the fourth to the eighth ribs. This rash remained for three or four days.

CASE 2—H W, negro, native of Grenada, ward attendant. He received an injection of horse serum June 23, 1905. The secondary injection was received Oct 18 1911. Erythema at the point of inoculation was noted October 19. On the night of the twenty-sixth urticaria appeared and the patient awoke on the morning of the twenty-seventh at 2 a m, feeling "stified." He took a drink of water and became covered with sweat. Could not go on duty this morning and remained off duty the twenty-eighth and twenty-ninth. Sticking pains in the chest were felt on the night of the twenty-sixth and twenty-seventh. Fainting sensations were experienced on getting out of bed or on taking an erect position after stooping over. On October 30 he returned to duty and for two or three days felt weak and sore in all his muscles.

H C C, who also developed symptoms of serum disease, was exposed to the case of plague of Oct 17, 1911, and received on October 18, 10 cc of Yersin's antipest serum. October 20, local ("specific") urticaria appeared at the site of inoculation. October 26 there was swelling of the arms, face and hands with more urticaria at the point of inoculation, and slight vertigo on rising.

H C C had received horse serum previously, September, 1906, 5 cc + — diphtheria antitoxin. September, 1906, 5 cc + — diphtheria antitoxin. October, 1906, 15 to 20 cc + — diphtheria antitoxin.

Shortly after the October (1906) injection local urticaria of the thigh appeared, and ten days after the injection of serum there was tremendous universal edema, with edema of the throat and larynx, causing some anxiety among his confreres. Between October, 1906, and April, 1907, he received diphtheria antitoxin several times, and on one occasion had a measles-like rash.



In this small series of cases of anaphylactic serum disease, only three of the seventeen individuals receiving serum experienced any symptoms of serum disease, and each one of these three persons had previously been sensitized by injections of horse-serum S T D and H W six years and four months, and H C C five years previously. On this last occasion, H C C had a late "immediate" (?) and an "accelerated" reaction. S T D had an "accelerated" reaction and H W had a late "accelerated" reaction.

Considering the fact that the only individuals who suffered from serum disease were those who had been sensitized by previous injections of horse-serum, and on account of the very disagreeable symptoms and consequent loss of time from business, together with the doubtful value of Yersin's serum in preventing or aborting an attack of plague, its indiscriminate use for the immunization of contacts is considered inadvisable.

# THE PATHOGENESIS OF PURPURA HEMORRHAGICA WITH ESPECIAL REFERENCE TO THE PART PLAYED BY BLOOD-PLATELETS

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The hemorrhagic diathesis of chloroform and phosphorus poisoning is without doubt due to a deficiency of fibrinogen in the blood and that of a type of melena neonatorum to a retarded rate or complete failure of blood coagulation. The hemorrhages of jaundice and hemophilia can perhaps be accounted for by abnormal blood coagulation, although proof of this is not so clear as in the former diseases. The disease with which I shall deal in this paper, namely purpura hemorrhagica, has apparently an entirely different pathogenesis and, it is believed, is due wholly or partly to an almost complete absence of platelets from the blood.

## HISTORICAL REVIEW

That the number of platelets in the blood is reduced in purpura hemorrhagica was first observed in 1887 by Denys, a histologist, and later by Hayem, the discoverer of blood-platelets. Denys<sup>1</sup> reported three cases in which platelets could hardly be found in fresh blood films. Hayem,<sup>2</sup> in three cases of idiopathic purpura hemorrhagica, made counts of 89,900, 62,000 and 41,000, and in two cases of symptomatic purpura hemorrhagica reported with Bensaude,<sup>3</sup> noted a scarcity of platelets in blood films. Bensaude and Rivet,<sup>4</sup> working in Hayem's clinic, studied stained and fresh blood films in five cases of chronic purpura hemor-

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<sup>1</sup>Results reported in brief before the Johns Hopkins Medical Society, Feb 19, 1912

1 Denys, J (a) *Études sur la coagulation du sang dans un cas de purpura avec diminution considérable des plaquettes* La Cellule 1887, III, (b) *Un nouveau cas de purpura avec diminution considérable des plaquettes* La Cellule 1889, v, 189, (c) *Blutbefund und Culturversuche in einem Fall von Purpura hamorrhagica* Centralbl f Path u path Anat, 1893, iv, 174

2 Hayem, G *Du purpura*, Presse méd, 1895, 233

3 Hayem, G, and Bensaude, R (a) *Leucémie aigue à forme de purpura hémorrhagique* Non-retractilité de caillot sanguin Bull et mém Soc méd d hôp de Paris, Feb 13, 1903, (b) *Sur la non-rétractilité du caillot et l'absence de formation de sérum dans la variole hémorrhagique primitive* Mécanism des hémorragies Soc de biol, Jan 19, 1901

4 Bensaude, R, and Rivet, L *Les formes chroniques du purpura hémorrhagique*, Arch gén de méd, January, 1905

rhagica and stated that the platelets were reduced in number Coe,<sup>5</sup> in five cases of hemorrhagic diathesis, found a reduced number of platelets. Three of his counts were 29,000, 22,000 and 25,000. The other determinations were made by examining stained blood-smears. Helber<sup>6</sup> observed a case of purpura hemorrhagica in which the platelet count was 40,000. Ehrlich<sup>7</sup> and Muller<sup>8</sup> each report having seen a case similar to those reported by Denys. Pratt,<sup>9</sup> in a case of purpura hemorrhagica complicating nephritis, made a count of 9,000. Selling,<sup>10</sup> in studying purpura hemorrhagica complicating benzol poisoning, found in one instance a platelet count of 3,000. In another he noted an almost complete absence of platelets from blood-smears. Matthews and Carpenter,<sup>11</sup> in a convalescent case of purpura hemorrhagica found the count to be 18,700. Larrabee,<sup>12</sup> in two cases of hemorrhagic diathesis in aplastic anemia, found a scarcity of platelets in blood-smears. In a previous paper<sup>13</sup> I reported three cases of severe hemorrhagic diathesis in which platelet counts made during periods in which pathologic hemorrhage was present were all below 32,000. In each of these cases a large number of platelets were introduced into the circulation by direct transfusion of blood. Immediate and complete relief followed this procedure and persisted until the platelets introduced had disappeared. When the counts reached their previous low levels hemorrhage returned. The period of relief was attributed directly to the increased number of the blood-platelets.

A few low platelet counts have been reported in patients in whom hemorrhagic diathesis was not evident. Osler,<sup>14</sup> Riess<sup>15</sup> and others have found them reduced in pernicious anemia, Determann,<sup>16</sup> in a case of nephritis (88,000) and in a case of pneumonia (40,000). Low counts

5 Coe, J. N. The Treatment of Purpuric Conditions and Hemophilia. *Jour Am Med Assn*, 1906, xlvii, 1090.

6 Helber, E. Ueber die Zahl der blutplättchen im Blute des Menschen und ihr Verhalten bei pathologischen Zuständen. *Deutsch Arch f klin Med*, lxxxii, 317.

7 Ehrlich. *Die Anämie*, 1898, 134.

8 Muller, H. F. Ueber einen bisher nicht beobachteten formbestandteil des Blutes. *Centralbl f allg Path u path Anat*, 1896, vii, No 13, p 531.

9 Pratt, J. H. *Osler's Modern Medicine*, 1907, iv, p 681.

10 Selling, L. A Preliminary Report of Some Cases of Purpura Hemorrhagica Due to Benzol Poisoning. *Bull Johns Hopkins Hosp*, 1910, xxi, 33.

11 Matthews, A. C., and Carpenter, H. P. Purpura Hemorrhagica with Report of an Atypical Case. *Am Jour Med Sc*, July, 1911.

12 Larrabee, R. C. Aplastic Anemia, with Report of a Case. *Am Jour Med Sc*, July, 1911.

13 Duke, W. W. The Relation of Blood Platelets to Hemorrhagic Disease. *Jour Am Med Assn*, 1910, iv, 1185.

14 Osler, William. Cited by Riess, Note 15.

15 Riess, L. Bemerkungen über die Zerfallskörperchen des Blutes und ihr Verhältniss zur Anämie. *Berl klin Wchnschr*, 1879, xvi, 696.

16 Determann. Klinische Untersuchungen über Blutplättchen. *Arch f klin Med*, 1898, ix, 365.

have also been found in lymphocytic leukemia, aplastic anemia and typhoid fever. Hayem, Riess, Wright and Kinnicutt and others found the platelet count reduced during the febrile period of several acute diseases. Hayem states that his lowest counts were in cases of purpura hemorrhagica.

#### GENERAL CONSIDERATIONS

It was seen early in this work that patients with purpura hemorrhagica of the type associated with an enormously reduced platelet count had a tendency to bleed from every trivial abrasion of the skin or mucous membranes. Frequently it was noticed that a patient bled for hours from a prick in the lobe of the ear or from a mere scratch on the skin. In some cases even the chewing of coarse food caused the gums to bleed. A slight blow, or even the rubbing or scratching of the skin, resulted in the formation of ecchymoses. Patients entering the hospital with severe symptoms were improved by the avoidance of all possible injury. In some cases extensive purpura cleared and hemorrhage from mucous membranes stopped almost completely following simple rest in bed. That there was little or no change in the general condition to account for this improvement was evidenced by the fact that a prick in the lobe of the ear would bleed for several hours. It seemed obvious that the observation of symptoms alone would lead to false conclusions as to the severity of hemorrhagic diathesis. It was several times noted, for example, that ambulatory patients with the disease in mild form displayed more purpura and more profuse hemorrhage from mucous membranes than the severer hospital cases. For this reason conclusions in this study have been based but partly on symptoms shown by the patient. More reliable data was gained by observing their tendency to bleed from fresh cuts. This was studied by a means outlined briefly by me in a previous paper<sup>13</sup> and called "the bleeding time."

#### THE BLEEDING TIME

The bleeding time is determined as follows. Make a small cut in the lobe of the ear. At half minute intervals blot up on absorbent paper all the blood which has flowed out. This gives a series of blots. Each blot represents the volume of blood flowing out in its respective half minute. From the rate of decrease in the size of the blots one can see at a glance the rate of decrease in the intensity of the hemorrhage. The duration of such a hemorrhage is called the bleeding time.

On first thought one might believe that the bleeding time depends largely on the size of the cut. This, however, within certain limits, is not the case. Figure 1 (a, b, c) are three normal bleeding times obtained from cuts of different sizes. The blots obtained from the largest cut (c) decrease in size even more rapidly than those obtained from the smallest cut (a). If hemorrhage from these cuts can be considered capillary hemorrhage, it is evident that a large number of capillaries stop bleeding

as rapidly as a small number. In marked contrast to the above is the prolonged bleeding time shown in Figure 2. This bleeding time was obtained from the smallest needle prick. The twentieth blot is practically as large as the first. Such a hemorrhage has been known to continue for more than two hours.

When the blots decrease rapidly in size the bleeding time is considered normal (one to three minutes). When they decrease more slowly in size and stop in from five to ten minutes it is considered slightly prolonged. Such is occasionally seen in severe anemia. When the twentieth blot is half the size of the first the bleeding time is moderately prolonged, and when as large as the first, is enormously prolonged.

The bleeding time is practically never more than slightly prolonged in normal individuals — at least such has been my observation during a period of three years.

It is prolonged in some types of hemorrhagic disease and not in others. It is enormously prolonged in chloroform poisoning when the decrease in the fibrinogen content of the blood is great. It is also enormously prolonged in purpura hemorrhagica of the type associated with a reduced platelet count. In these two diseases the bleeding time gives reliable information as to the severity of the hemorrhagic diathesis. It usually ranges from twenty minutes to several hours when the symptoms are severe, and drops to normal the moment the condition is relieved.

The bleeding time in my experience is normal in all forms of purpura simplex and jaundice. Observations have been made on patients with the following varieties of purpura: simplex, idiopathic purpura simplex, purpura secondary to nephritis and septicemia, purpura rheumatica, Henoch's complex, scurvy, senile purpura, cachectic purpura, and purpura showing a segmental distribution. Observations have been made on patients with jaundice associated with a normal coagulation time and no hemorrhage, with a slightly delayed coagulation time and severe purpura hemorrhagica, and with an enormously prolonged coagulation time (thirty minutes and more) with and without evidence of pathologic hemorrhage. In all the above patients the bleeding time was less than three minutes. The platelet count was normal or slightly increased.

The bleeding time is, therefore, limited in its usefulness and can be employed to advantage in certain types of disease only.

#### OTHER METHODS

The coagulation time was determined by a simple method described by me<sup>13, 17</sup> in previous papers.

The fibrinogen content of the blood in humans was estimated roughly by observing the firmness of blood-clots. It was estimated quantitatively

<sup>17</sup> Duke, W. W. A Simple Instrument for Determining the Coagulation Time of the Blood. *THE ARCHIVES INT. MED.*, February, 1912, 18, 258.

in dogs by a heat precipitation method as described by Whipple and Huitwitz<sup>18</sup>

Retractility of the clot was studied as by Hayem<sup>2, 19</sup> Two c c of blood were collected in a small test-tube and allowed to stand at room temperature for forty-eight hours. Normally the clot separates itself in a short time from the sides of the vessel containing it and extrudes serum

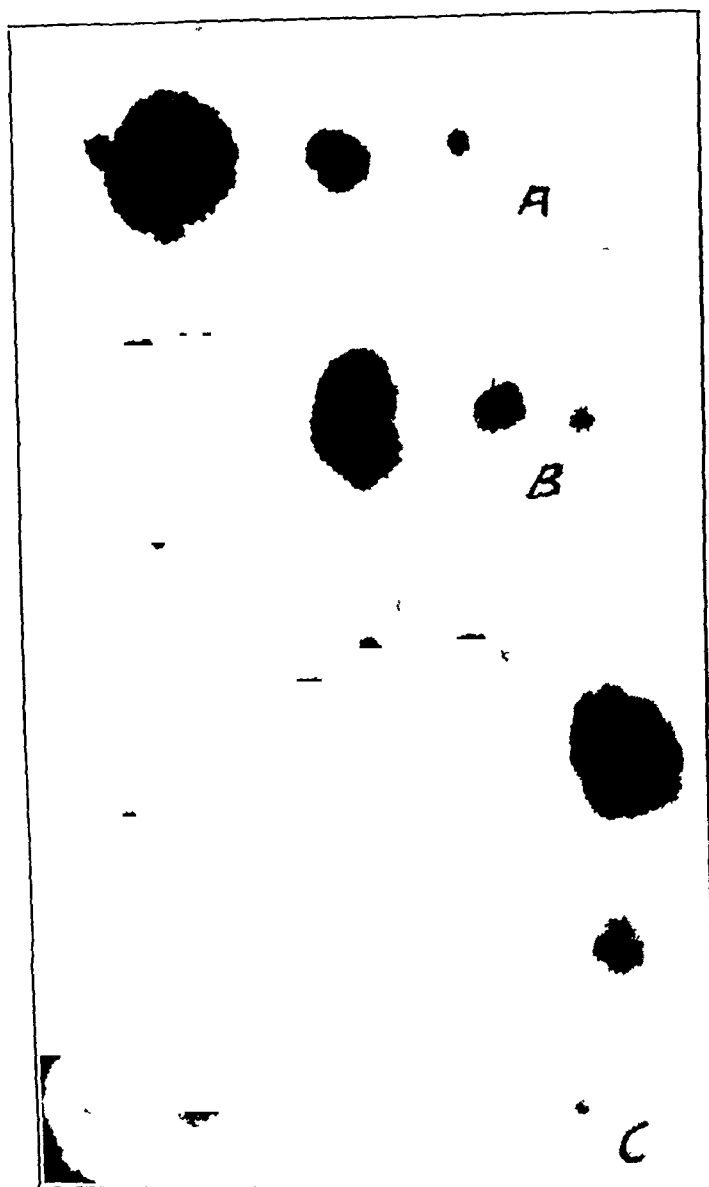


Fig 1—Normal bleeding times. A, from small cut, B, from larger cut, C, from very large cut

Under certain pathologic conditions retraction fails to take place and little or no clear serum can be seen

<sup>18</sup> Whipple G H and Huitwitz Jour Exper Med 1911 xiii, 136

<sup>19</sup> Hayem G Du Caillot non retractile Suppression de la formation du serum sanguine dans quelque états pathologique Compt rend Acad d sc, 1896, cxviii 894 Cited by Bensinde

The platelet counts were made by Wright and Kinnicut's method with precautions mentioned by me<sup>21</sup> in a previous paper. This presents several advantages over other methods. It is simple and can be carried out with the ordinary blood pipets and counting chamber. Platelets are stained by the diluting fluid and thus rendered easily countable. The red cells are bled. The limit of error in counting is somewhat greater than in red or white cell counts. The percentage variation in the platelet count is so great, however, that an error of 20 per cent may be considered negligible.

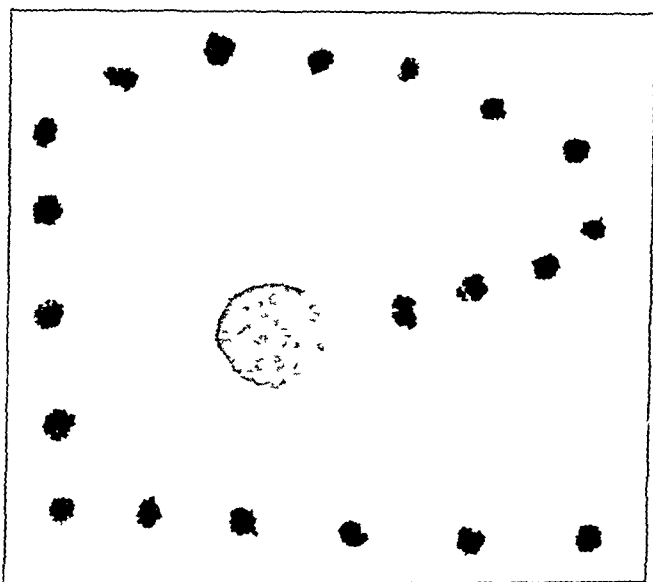


Figure 2

The following counts were made in four normal individuals

TABLE 1—NORMAL PLATELET COUNTS IN FOUR INDIVIDUALS

Date	I	II	III	IV
May 9	275,000	295,000	290,000	315,000
May 10				
May 11				
May 12	220,000	300,000	280,000	240,000
May 13				
May 14		280,000		
May 15		270,000		190,000
May 16	225,000	300,000	300,000	
May 17				220,000
May 18		240,000		190,000
May 19	230,000		350,000	
May 20	225,000		275,000	
May 21		260,000		
May 22	196,000		400,000	
May 23	220,000			
May 24	240,000		250,000	
Highest count	275,000	300,000	400,000	315,000
Lowest count	196,000	240,000	250,000	190,000
Average count	224,000	264,000	306,000	231,000

## REPORT OF CASES

In the following study an effort was made to find some relationship between hemorrhagic diathesis and the condition of the blood. Hemorrhagic symptoms, the bleeding time, the platelet count and blood coagulation were studied in all cases which displayed a pathologic tendency to bleed, seen during the past three years. In many of the cases no abnormality of the blood could be discovered. In a certain group, however, the platelet count was constantly and enormously reduced. This group differed in many respects from the group having normal counts, in fact,

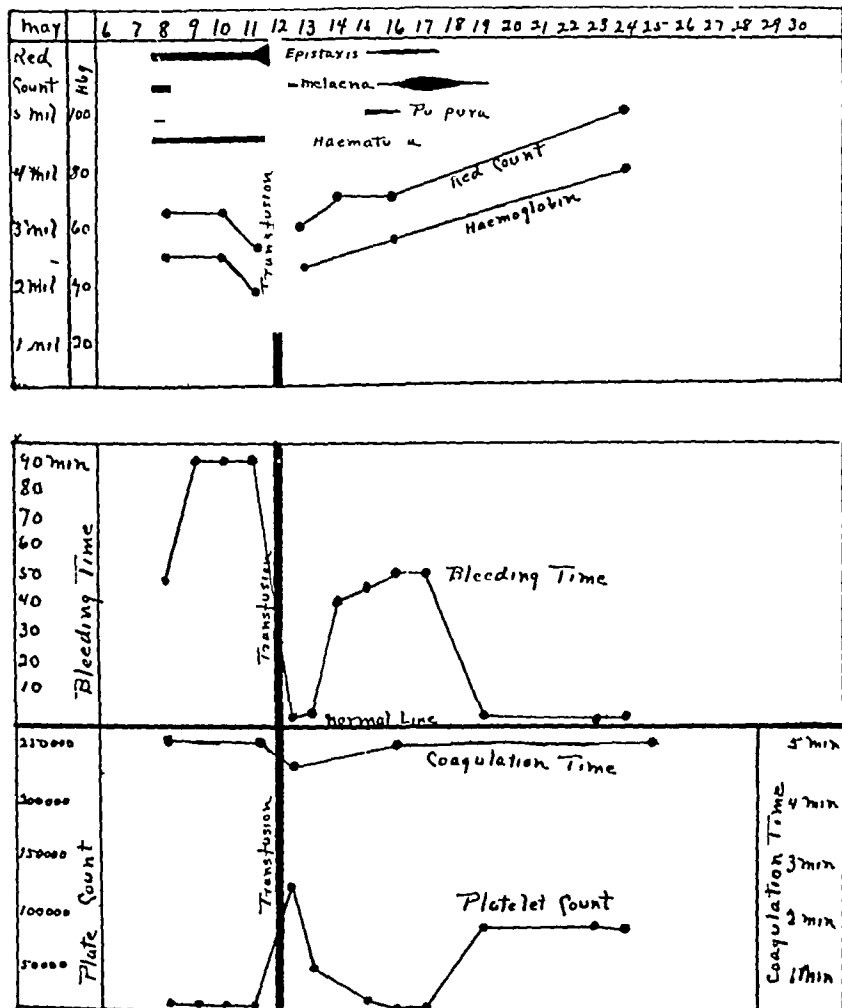


Fig 3—Chart of Case 1

it became possible from the history and examination of a patient with well marked hemorrhagic diathesis, to correctly predict whether the platelet count was about normal or was greatly reduced. Subsequent discussion will be confined to the platelet-free group of cases, a detailed report of thirteen of which is as follows:

CASE 1—*Idiopathic purpura hemorrhagica with result of transfusion* (Case observed in the Massachusetts General Hospital Boston for more complete report of which see reference 13.)



*History*—S M man aged 20 tailor Family and past history unimportant For four days before admission to the hospital the patient suffered from malaise, epistaxis bleeding from the gums, hematuria, melena and had noticed a purpuric rash Results of physical examination unimportant except for pallor and a generalized fine petechial rash Petechias were seen even on the conjunctiva, mucous membrane of the mouth, the soles of the feet

*Laboratory Examination*—Stools and urine not remarkable except that they contained a considerable quantity of blood

Platelet count 6 000 Bleeding time 60 minutes Coagulation time normal (5 minutes) Clot firm and non retractile

Leukocytes varied from 2,400 to 7 000 Polymorphonuclears 80 per cent to 86 per cent Remainder mainly lymphocytes One blast seen Erythrocytes on admission 3 264 000 Hgb 50 per cent Sahli Appearance of red cells normal

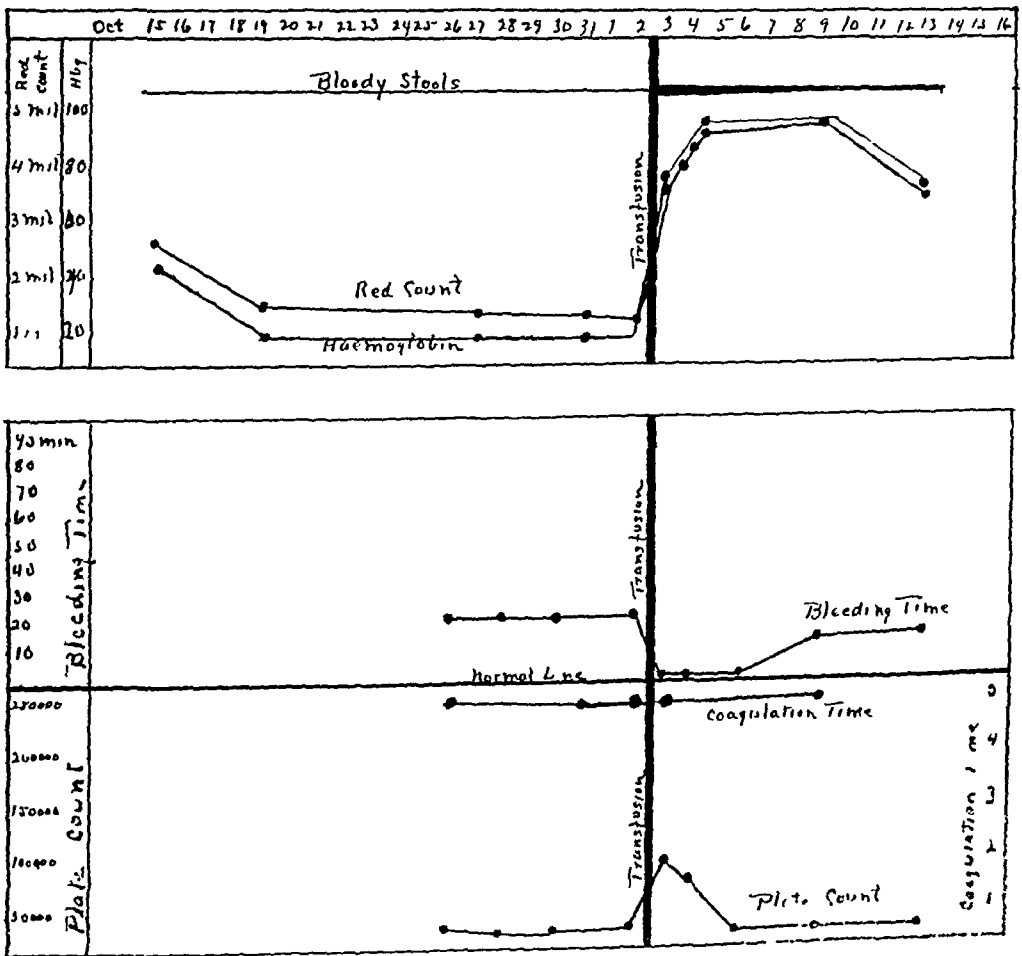


Fig. 4—Chart of Case 2

*Course of the Disease*—The symptoms and laboratory findings were practically unchanged during the first four days in the hospital. On the fifth day a direct transfusion of blood was successfully carried out by Dr. F. T. Murphy. Following this there was complete cessation of all hemorrhage and the purpuric flecks began to fade. The platelet count was increased by transfusion to 123,000. The bleeding time was reduced to normal. The coagulation time was unchanged. The clot was retractile.

The number of platelets in the blood decreased rapidly after transfusion and on about the fourth day reached its previous low level. At this time epistaxis

began again and fresh blood appeared in the stools. The bleeding time was again enormously prolonged. The coagulation time was unchanged. The clot was again non-retractile.

This condition continued practically unchanged for six days. On the seventh day there was complete cessation of epistaxis and there was no more blood in the stools. Platelets were present in the blood in abundance. The bleeding time was normal. The coagulation time was unchanged. The clot was normally retractile.

No purpura appeared during the second hemorrhagic period. The patient, during the following year, had no return of hemorrhage.

**CASE 2**—*Chronic intestinal bleeding in a boy with chronic ulcerative colitis*. Results of transfusion (Case observed in the Massachusetts General Hospital, Boston, for more complete report of which see Reference 13.)

**History**—A C, boy, aged 8. Family history negative. Since the age of 2 the patient had suffered almost continually from diarrhea. For four periods of a month or less, the stools contained considerable blood. The stools had contained blood for more than a month before admission to the hospital and the patient was pale and weak. Physical examination was unimportant except for pallor. There were no ecchymoses and no bleeding from normal mucous membranes while under observation. The stools contained mucus and pus and considerable fresh blood.

**Laboratory Examination**—Platelet count 32,000. Bleeding time moderately prolonged (20 minutes). Coagulation time 5 minutes, clot firm, retractility diminished.

Leukocytes 2,200 to 4,700. Polymorphonuclears 40 per cent to 60 per cent. Remainder mainly lymphocytes. Erythrocytes 1,600,000. Hgb 20 per cent. Appearance of reds normal. No blasts.

**Course of the Disease**—Symptoms and laboratory findings continued unchanged for seven days. On the eighth day direct transfusion of blood was successfully carried out by Dr. Hugh Cabot. The platelet count, made just after transfusion, was 89,000. The bleeding time was normal. The coagulation was unchanged. The clot was normally retractile.

The platelet count decreased steadily after transfusion, and on the fourth day had reached its previous low level. The bleeding time was then again prolonged. Conditions continued about the same until the boy's death, several weeks later.

**Comment** This case is of interest in showing a striking difference between the effect of transfusion on normal and pathologic hemorrhage. The amount of blood in the stools was increased by transfusion in spite of the fact that the general tendency to bleed, as shown by the shortening of the bleeding time, was less marked. The intestinal hemorrhage, as shown by autopsy, proceeded from extensive intestinal ulcerations and cannot, therefore, be considered entirely pathologic hemorrhage. The increased hemorrhage following transfusion was thought to be due to the increased filling of the blood-vessels.

**CASE 3**—*Severe purpura hemorrhagica in a man with phthisis* (Case observed in Professor Romberg's clinic, Tübingen.)

**History**—W F, man aged 26, a weaver. Family history good. Past history negative except for attacks of migratory polyarthritis at the ages of 17 and 19. At the age of 16 and 21 he had nose-bleed for a short time. For five months he had had symptoms of phthisis and was in the hospital for this.

**Physical Examination**—The patient was the picture of rather advanced phthisis. There were signs of considerable consolidation and possible cavity formation at both lung apices. The fingers were moderately clubbed. The daily temperature varied from 36 to 38 C.

*Present Illness*—On May 13 the platelet count made as routine was 210,000, and the bleeding time was normal. Four days later, without other change in symptoms, the patient had profuse epistaxis and bleeding from the gums. He had continued bleeding from a hang nail on the thumb, also hematuria, melena, and hemorrhages from acne lesions on the face. A fine petechial rash was present on the abdomen and legs. The slightest rubbing brought out new flecks.

*Laboratory Examination*—The bleeding time was enormously prolonged (over two hours). The platelet count was 4,000. Coagulation time normal (5 min.), clot firm and non retractile. Leukocytes 19,000. Polymorphonuclears 74 per cent. Lymphocytes 16 per cent. Eosinophils 10 per cent. Basophils 0 per cent. No blasts. Reds normal in appearance, size and shape. Hemoglobin 80 per cent, Sahli. Urine and stools normal except for the presence of fresh blood. Sputum contained many tubercle bacilli.

*Course of the Disease*—On the following day no platelets could be found, either in stained smears or in counting chambers. Their presence, in small numbers, was demonstrated, however, by examining the undiluted plasma by Burker's

TABLE 2—RESULTS OF DAILY EXAMINATION OF BLOOD IN CASE 3

Date	Platelet Count	Bleeding Time	Hemorrhages
May 14	210,000	Normal	None
" 17			Severe
" 18	4,000	Extreme delay	Severe
" 19	Below 1,000	Extreme delay	Severe
" 20	10,000	Extreme delay	Severe
" 21	Below 1,000	Extreme delay	Severe
" 22	110,000	Normal	None
" 23	210,000	Normal	None
" 24	295,000	Normal	None
" 26	385,000	Normal	None
" 27	520,000	Normal	None
" 28	550,000	Normal	None
" 30	720,000	Normal	None
June 1	720,000	Normal	None
" 7	640,000	Normal	None
" 12	400 000	Normal	None
" 17	500 000	Normal	None

method. Fibrin was present in abundance in this preparation and consisted of thick fibrils. There was no change in either symptoms or laboratory findings until May 22, when all hemorrhages ceased as suddenly as they had set in. The platelet count had suddenly increased to 110,000. The bleeding time had dropped to normal. The coagulation time was not noticeably changed. The clot was normally retractile. During the two months following there was no further bleeding.

The results of the daily examinations are contained in Table 2.

CASE 4—*Idiopathic purpura hemorrhagica* (Case observed in Professor Riehl's clinic, Vienna.)

*History*—J. S., man aged 33, postman. Family history unimportant. Scarlet fever at 10, sore throat at 21, no other illnesses. For the four days previous to admission to the hospital the patient had been troubled with epistaxis and had noticed a purpuric rash. History otherwise negative.

*Physical Examination*—A well developed and nourished man. Except for fine petechiæ scattered over face, body, legs and arms, nothing of importance was disclosed.

*Laboratory Examination*—For the platelet count and bleeding time, see Table 3 Coagulation time normal Clot firm and non-retractile White count varied from 3,000 to 13,000 Polymorphonuclears 35 to 50 per cent, remainder lymphocytes with occasional eosinophils and basophils No blasts Hgb 70 to 60 per cent, Sahli Appearance of reds normal Urine and stools not remarkable except for the presence of a considerable quantity of blood

*Course of the Disease*—The patient was under observation about one month During this time there was but little improvement After the first few days the stools and urine contained only traces of blood Numbers of fine petechiæ appeared at frequent intervals Submucous hemorrhages appeared frequently on the tongue, gums and cheeks, and from these would proceed small hemorrhages Slight epistaxis was present a considerable part of the time The bleeding time was always prolonged—at some times much more than others The shortening of the bleeding time and amelioration of hemorrhage bore possibly some relation to variation in the platelet count Counts, however, at a level of 10,000 are none too accurate, and it is perhaps unsafe to draw conclusions from them

TABLE 3—PLATELET COUNT AND BLEEDING TIME IN CASE 4

Date	Platelet Count	Prolonged Bleeding Time	Hemorrhage	Fresh Petechiæ on Skin
February—				
25	Under 1,000	Extreme	Much	Many
27	Under 1,000	Extreme	Much	Many
March—				
1	Under 1 000	30 min	Much	None
2	4,000	Extreme	Slight	None
3	9,000	7 min	Slight	None
4	5,000	Moderate	Slight	Mod number
5	1,000	Extreme	Slight	Mod number
6	Under 1,000	Extreme	None	Mod number
10	3,000	Moderate	None	None
11	2,000	Extreme	None	None
13	2,000	Extreme	Slight	None
14	6,000	12 min	Slight	None
15	9,000	10 min	Slight	None
16	7,000	8 min	None	None
17	2,000	Extreme	Slight	Many
18	6,000	7 min	Slight	None
19		Extreme	Slight	Many
20	Under 1,000	Moderate	Slight	Many

One of the most striking features of the case was the patient's good general condition and freedom from symptoms other than hemorrhage

CASE 5—*Epistaxis in a woman with phthisis* (Case observed in Professor Romberg's clinic, Tübingen)

*History*—K, woman aged 35, housewife Family and past history negative for hemorrhagic disease For several months the patient had had symptoms of rather rapidly advancing phthisis For three days she had had epistaxis History otherwise unimportant Physical examination disclosed considerable consolidation at lung apices with possible cavity formation Nothing further of importance Daily temperature varied from 37 to 40 C

Slight epistaxis continued for four days and then ceased This and the prolonged bleeding time were the only evidences of hemorrhagic diathesis (For the platelet count and bleeding time see Table 4)

CASE 6—*Ecchymoses and epistaxis in a man with aplastic anemia* (Case observed in Professor Riehl's clinic, Vienna)

*History*—Man, aged 27, clerk Family and past history negative for hemorrhagic disease For six months the patient had been troubled with subcutaneous swellings which appeared first on the cheeks and later on the lips and front of the chest He had been troubled with an occasional slight epistaxis and had noticed a discoloration of the skin over many of the tumors

TABLE 4—PLATELET COUNT AND BLEEDING TIME IN CASE 5

Date	Platelet Count	Prolonged Bleeding Time	Epistaxis
May 12	55,000	Moderate	Slight
" 13	50,000	Moderate	Slight
" 15	65,000	Moderate	Slight
" 18	75,000	Slight	None
" 20	80,000	Normal	None
" 23	88,000	Normal	None
" 29	74,000	Normal	None
June 2	130,000	Normal	None
" 12	150,000	Normal	None
" 17	190,000	Normal	None

*Physical Examination*—A pale, emaciated man with subcutaneous growths involving mucous membrane of nose and lips, skin of cheeks, chest and abdomen Over most of the tumors were blue to yellow discolorations of the skin The tumors were histologically cellular infiltrations of the subcutaneous tissue of unknown character Physical findings otherwise of no interest in this connection

*Laboratory Findings*—For platelet count and bleeding time see Table 5 White count varied from 7,000 to about 500 Of these 50 per cent to 90 per cent were lymphocytes, the remainder polymorphonuclears with an occasional eosinophil and

TABLE 5—BLOOD FINDINGS IN CASE 6

Date	Platelet Count	Bleeding Time	Leukocytes
Feb 7	22,500	5 min	2,000
" 9	19,500	5 min	below 1,000
" 14	94,500	2 min	2,500
" 18	177,000	1 min	
" 20	216,000	1 min	7,000
" 24	180,000	1 min	3,000
" 27	120,000	1 min	5,000
Mar 11	165,000	1 min	5,500

basophil No blasts Red count 3,500,000, Hgb 50 per cent, Sahli, red count and Hgb did not vary markedly while the patient was under observation Reds varied slightly in size and shape No stippling The urine and stools contained no blood

*Course of Disease*—During the first few days in the hospital the patient had slight epistaxis, after this, none The discolorations of the skin began to fade soon after entering the hospital The blood-picture in this case was of great interest but cannot be dealt with at length in this paper

CASE 7—*Chronic purpura hemorrhagica, in a girl with prolapse of the rectum* (Case observed in the New York Hospital See Reference 13 for more complete report of case )

*History*—Georgiana, girl, aged 3 One sister was born with a petechial rash, family history otherwise negative The patient has several times had prolapse of the rectum Since the age of 19 months she has been subject to nose bleed and ecchymosis on slight injury On two occasions epistaxis was so severe and prolonged that her life was almost despaired of On one of these occasions direct transfusion of blood was carried out by Dr R D McClure Following this there was complete cessation of hemorrhage for three days On the fourth day she had slight hemorrhage from the nose, vagina and transfusion wounds On one occasion a fine generalized petechial rash appeared after straining at stool The patient came under observation once with varicella Each vesicle was surrounded by a small subcutaneous hemorrhage

At the time of the one blood examination, the patient was subject to epistaxis and had on her face and body several large ecchymoses The platelet count was then below 10,000, bleeding time over one hour, coagulation time normal, clot firm and non-retractile

At the time of another examination, no evidence of hemorrhage could be found Platelets were then present in abundance Bleeding time 5 to 10 minutes Clot retractile

CASE 8—*Severe purpura hemorrhagica in child with diphtheria* (Case observed in Professor Escherich's clinic, Vienna )

*History*—A E, boy aged 6 Family and past history negative for hemorrhagic disease

*Present Illness*—For several days before admission to the hospital the child had had sore throat For two days the mother had noticed ecchymoses about the face For one day he had had epistaxis

*Physical Examination*—The child was extremely toxic and ill Examination of the throat disclosed a typical diphtheritic membrane On the face were several ecchymoses, 2 to 4 cm in diameter

*Laboratory Examination*—Platelet count 3,000, bleeding time extremely prolonged, coagulation time normal, clot firm and non-retractile, white count 75,000

The patient died two days later Anatomical diagnosis, pharyngeal diphtheria, toxic myocarditis, toxic nephritis

CASE 9—*Chronic purpura hemorrhagica in a woman with gastro intestinal trouble* (Case observed in Prof von Noorden's clinic, Vienna )

*History*—J W, maid aged 37, cook Family history negative for hemorrhagic disease

*Past History*—Migratory polyarthritis at age of 18 She has always been subject to attacks of tonsillitis Since the age of 25 she has had considerable stomach trouble, especially during the summer months Main complaints were pain, usually at its worst at night, anorexia, nausea and vomiting She has always been troubled with constipation and has frequently seen mucus in the stools Never noticed blood in stools nor vomitus

*Present Illness*—Since childhood she has been subject to epistaxis and ecchymosis following slight injury Since her stomach trouble began this tendency has been much worse, and like the stomach trouble, is at its worst during the summer months Has for periods had epistaxis, bleeding from the gums, profuse menstruation and has been almost covered with ecchymoses When patient came under observation hemorrhagic symptoms were mild Main complaint was stomach trouble, constipation and menorrhagia Physical examination disclosed nothing of importance except a few small blue and yellow ecchymoses scattered over the body The uterus was normal in size and position

*Laboratory Examination*—Test meal not remarkable except for slight hyperacidity Urine and stool not remarkable Platelet count 9,000 Bleeding time, twelve minutes Coagulation time five minutes Clot firm and non-retractile Leukocytes 9,000 Polymorphonuclears 91 per cent Lymphocytes 8 per cent No blasts Hgb 90 per cent S Reds normal in appearance One week later the platelet count was as before, 9,000 The bleeding time was eight minutes There had been no marked change in the symptoms

CASE 10—*Few ecchymoses in a man with alcoholic cirrhosis of the liver, chronic interstitial nephritis, secondary anemia*

The patient, at the time of examination, had several ecchymoses around the knee, which had appeared without adequate cause No other evidence of hemorrhagic disease

Platelet count, 50,000 Bleeding time normal

CASE 11—*Hematemesis in a man with cirrhosis of the liver*

At the time of examination the patient was vomiting blood, and had tarry stools In this case there was no definite evidence of hemorrhagic disease

Platelet count 60,000 Bleeding time normal

CASE 12—*Epistaxis in a man with malignant syphilis*

The day preceding the blood examination, the patient had had severe epistaxis No local cause for bleeding found

Platelet count 65,000 Bleeding time normal

A few weeks after the above examination the patient had tuberculous peritonitis

(Cases 10, 11, 12 were observed in Prof Romberg's clinic, Tübingen)

CASE 13—*Severe purpura hemorrhagica in a man with aplastic anemia (proved at autopsy)* (Case observed in private practice)

The patient at the time of examination had bleeding from the gums and severe epistaxis Several large ecchymoses were scattered over the body

Plates very scarce in fresh and stained blood-preparations Bleeding time moderately prolonged

#### SUMMARY OF CASES

The severer of the cases were examples of purpura hemorrhagica and presented the following symptom complex

1 Purpura, usually present, conformed to two distinct types—ecchymoses and petechias The ecchymoses, evidently brought out by mechanical agents such as slight blows, rubbing, etc., presented a varied appearance In some instances they were simply small bruises, in others large, elevated, indurated, blue to yellow areas over 35 cm in diameter Their appearance was dependent partly on the nature of the injury which brought them out, partly on the intensity of the hemorrhagic diathesis The petechias often developed without local mechanical cause When such was the case they consisted of small flecks, 1 to 3 mm in diameter, were more or less uniform in size, had usually a very general, and sometimes an almost universal, distribution They were observed even on the scalp, soles of the feet, conjunctivæ, mucous membrane of the mouth, etc They were, as a rule, most abundant on the dependent parts and in these localities were frequently confluent, forming flat blue to yellow flecks—1 to 2 cm in diameter Petechias, although often appearing without apparent local cause, were not entirely independent of mechanical influence They were frequently brought out by rubbing, scratching, etc In

one patient, a fine petechial rash appeared immediately after straining at stool (Case 7). A petechial rash was most commonly observed in patients who were up and about and working, and frequently faded rapidly when they were confined to bed. The latter observations make it seem that changes in capillary blood-pressure play some rôle in the production of this rash.

The appearance of the purpura was modified by the co-existence of other skin lesions and sometimes gave rise to peculiar appearances. For example, in a patient with chicken-pox (Case 7), a small area of purpura surrounded each vesicle. In a patient with acne rosacea (Case 3) each pustule was the site of a small hemorrhage. In a patient who presented numerous peculiar subcutaneous tumors there was a blue to brown discoloration of the skin over each growth (Case 6).

2 The ecchymoses were frequently, and the petechias almost always, accompanied by bleeding from one or more mucous surfaces—in fact, epistaxis, bleeding from the gums, etc., were the symptoms usually first noticed by the patient. Often bleeding proceeded from trivial abrasions of the mucous membranes, sometimes from petechias in the mucous membrane and occasionally oozed from membranes on which no lesion could be discovered.

3 The bleeding time was in all cases prolonged, usually very much so. It exceeded one hour, as a rule, when symptoms were severe, and dropped to normal as soon as the condition was relieved. This is one of the most constant and distinctive features of this disease. It is the consequence of a tendency which these patients have to bleed profusely from every vascular lesion no matter where or how produced. For example, one patient, with a bleeding time exceeding two hours, bled for hours from a hang nail on the thumb, bled profusely from acne lesions on the face, the chewing of coarse food caused the gums to bleed, there was blood in the urine and stools, and the rubbing or scratching of the skin brought out petechias.

4 The platelet count, in all severe cases, was reduced to the point of almost total absence. It did not exceed 10,000 in a single instance, and frequently was so low that platelets could be found neither in stained smears nor in counting chambers. In two instances in which it was believed from the above examinations that platelets were totally absent, the undiluted plasma was studied by Burker's method<sup>22</sup> and the presence of a few platelets demonstrated. As previously stated, the count was always excessively low while the general symptoms were severe. In every case, a rise in the count was accompanied by marked amelioration or complete relief of hemorrhagic diathesis. As a rule, the rise occurred

<sup>22</sup> Burker K. Eine einfache Methode zur Gewinnung von Blutplättchen. *Centralbl f. Physiol.*, June 20, 1903.



spontaneously, but in three cases (Cases 1, 2 and 7) it was evidently the direct result of transfusion. In these cases, the tendency to bleed returned as soon as the count reached the low level which existed prior to transfusion. In one instance (Case 4) platelet counts were made almost daily for a period of twenty-four days. In this case the tendency to bleed was most marked when the count was below 1,000, and amelioration of symptoms was noticeable whenever it rose to 9,000. The percentage of error in counting platelets is greater when the count is extremely low than when it is about normal. It is hardly safe, therefore, to draw conclusions from such slight variations.

5 In every case the coagulation time fell within normal limits. No striking variation in this either with the platelet count or with the severity of hemorrhagic diathesis was noted.

6 The clot was firm in every case.

7 The clot was non-retractile in every case so long as the platelet count was extremely low, and showed more or less retractility as soon as the count rose.

Many of the symptoms just mentioned were lacking in the milder cases, in fact, in these the diagnosis of the condition rested on the finding of a low platelet count. The symptoms most frequently complained of were small ecchymoses and epistaxis. Frequently neither was observed and the possibility that hemorrhagic diathesis existed was suggested simply by the fact that hemorrhage was present and seemed somewhat too severe or prolonged to be entirely accounted for by its local cause. Such hemorrhages were, for example, continued bleeding from intestinal ulcers (Case 2), profuse hemorrhage from esophageal varices (Case 11), profuse and prolonged menstruation (Case 9), etc.

The bleeding time in the milder cases was in some instances normal, and in others slightly or moderately prolonged. The platelet count fell between 19,500 and 60,000. The coagulation time was within normal limits. The clot was firm, and as a rule, gave diminished retractility.

There can be little doubt that the mild and the severe cases, differing as much as they did in hemorrhagic manifestations, are examples of one and the same disease, differing only in degree.

The entire symptomatology of the condition may be summarized by stating that in this disease there exists a tendency to bleed from every vascular lesion, no matter how produced. In severe cases an elevation of capillary blood-pressure by exercise, straining, etc., a rubbing or scratching of the skin, the presence of inflammatory lesions or of minute cuts or other abrasions of the skin are sufficient to produce purpura or prolonged hemorrhage. In mild cases, however, more severe lesions are required to produce the same phenomena. It is extremely interesting to find that a consistent tendency to bleed is not more frequently observed

in the other types of hemorrhagic diathesis. Such is the exception and not the rule. As mentioned, when discussing the bleeding time, we have observed patients with jaundice who bled profusely after operation and yet had a normal bleeding time and no purpura. The same observation was made on a patient with hemophilia. A patient with jaundice, ecchymoses, epistaxis and blood in the urine and stool gave a normal bleeding time. Several patients with purpura simplex who were almost covered with large ecchymoses had no hemorrhage from mucous membranes and would hardly bleed at all when the ear was pricked. All of the patients just mentioned gave high platelet counts.

#### THEORETICAL CONSIDERATIONS AND EXPERIMENTAL RESULTS

The following facts have led me to believe that an absence of blood-platelets plays an essential rôle in the pathogenesis of the type of purpura hemorrhagica with which we are here dealing.

1 Every case of pathologic hemorrhage observed by me, which presented a certain clinical picture (purpura, bleeding from mucous membranes, a prolonged bleeding time, a normal coagulation time and a firm blood-clot) had enormously reduced platelet counts. The tendency to hemorrhage vanished when the platelet count rose to a certain point, and reappeared when the count fell. The first observation was alike true, whether the rise in the count occurred spontaneously (Cases 3, 4, 5, 6) or was the direct result of transfusion (Case 1, 2 and 7).

2 A large number of platelet counts were made by me in three diseases (diphtheria, tuberculosis and nephritis) in which purpura hemorrhagica of the type here described was thought to be a complication. The typical disease-picture appeared in two instances (Cases 3 and 8) and in only two. In both of these cases the platelet counts were below 3,000. These were the lowest counts found in this series of cases. In a third case (Case 5) the count, for a few days, varied between 55,000 and 65,000. The patient at this time had mild hemorrhagic diathesis (epistaxis and a moderately prolonged bleeding time). Three rather low counts (40,000, 60,000, 75,000) were observed in patients with diphtheria who presented no evidence of hemorrhagic disease. These results with others, which will be reported later, indicate that 40,000 to 75,000 is a level at which patients may or may not have a mild disposition to bleed. A marked reduction below this, however, has been in my experience without exception accompanied by hemorrhagic diathesis.<sup>23</sup>

3 Purpura hemorrhagica occurs as a complication in a varied collection of diseases, all of which possess one feature in common—a liability

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<sup>23</sup> The cases of purpura hemorrhagica reported by Hayem and Helber gave counts (40,000 to 89,000) higher than any observed by me when the estimation was made at a time when bleeding was severe. This variance in results is possibly due to differences in the methods employed for counting.

to reduction in the number of platelets Hayem and Bensaude<sup>3, 24</sup> have observed it complicating lymphocytic leukemia, hemorrhagic small-pox and tuberculosis, Pratt<sup>9</sup> complicating nephritis, Selling<sup>10</sup> complicating aplastic anemia due to benzol poisoning, I have found it complicating diphtheria (Case 8), tuberculosis (Case 3) and aplastic anemia (Case 13) I have also observed it in a more or less severe form in patients suffering from chronic ulcerative colitis (Case 2), prolapsus of the rectum (Case 7), cirrhosis of the liver (Cases 10 and 11) and in a gastrointestinal condition (Case 9), which seemed to be spastic constipation associated with gastric hyperacidity

4 I have been able to produce severe hemorrhagic diathesis in animals by reducing the platelet count by means of diphtheria toxin and mild hemorrhagic diathesis with benzol The condition appeared only in the animals in which the platelet count was enormously reduced It became apparent at the time when the platelets disappeared from the circulation and was relieved when the platelet count rose These results will be reported in detail in a later paper One very interesting result was the following

#### EXPERIMENTAL PURPURA HEMORRHAGICA

Experiment 34—Male rabbit, weight 2.5 kg

Diphtheria toxin given in small doses (June 14 to 17, 1911), until the animal appeared to be somewhat ill The animal speedily recovered from the effects of the toxin and showed no further untoward symptoms On June 26th, that is, nine days after the last dose, it was noted for the first time that hemorrhage, resulting from a prick in an ear vein, was almost impossible to check The bleeding time, obtained by shaving the skin of the back and cutting fairly well through it with a razor, was excessively prolonged The fortieth drop of blood was almost as large as the first, that is, the flow of blood, after a period of twenty minutes, showed almost no diminution in intensity The bleeding time, when tested similarly in other animals, was one minute or less, in fact, in many instances the blood would hardly flow spontaneously at all On the following morning the hair covering the ear and back of the animal was matted with blood and the cage was everywhere spattered with blood A similar result was noted in no other of thirty-eight experiments Numerous subcutaneous hemorrhages in the ears were then noted for the first time This eruption was quite striking Some of the hemorrhages were about 0.5 cm in diameter—the majority were petechial, 1 to 3 mm in size These were distributed regularly over both ears, being as numerous over the areas which had not been punctured for obtaining blood as over the areas which had been shaved and pricked No purpura could be found on the surface of the body Such hemorrhages were seen in none of the other animals Blood collected in a test tube clotted quickly, but failed to retract and extrude serum even after standing four days The animal was at this time quite anemic and remained so as long as observations were continued The hemoglobin was 25 per cent The white count 16,000 Polymorphonuclear cells 60 per cent Lymphocytes 40 per cent No blasts were seen

The prolonged bleeding time and excessive hemorrhage from pricks in the ear veins continued unchanged for three days, that is, up to June 29 On this date the bleeding time was less prolonged, the twentieth drop was about half the size

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<sup>24</sup> Bensaude, R, and Rivet, L Purpura hémorragique et tuberculose Presse méd, July 25, 1906

of the first, and the hemorrhage from pricks in the ear veins was less profuse. The platelet count at this time had risen to 64,000 and continued to rise. The following day the bleeding time showed only a slight delay and after that was always normal. The bleeding from pricks in the ear veins was never again profuse. The animal, during the following week displayed no tendency to excessive hemorrhage. The data in detail are given in Table 6.

Except for the absence of epistaxis, this was a perfect experimental reproduction of the purpura hemorrhagica which complicated diphtheria (Case 8). It was evidently the same condition both etiologically and pathogenetically. All of the distinctive features were present, purpura, prolonged bleeding time, an extremely low platelet count, blood which clotted quickly, gave a firm clot, and failed to retract and extrude serum. The disease appeared the day the platelet count dropped to an extremely low level (4,000), persisted as long as the platelet count remained low, and

TABLE 6—PLATELET COUNT IN THE AUTHOR'S EXPERIMENTAL CASE

Date	Platelet Count	Remarks	Date	Platelet Count	Remarks
June—			June—		
13	430,000		26	4,000	Purpura hemorrhagica
14	620,000	Toxin S C	27	4,000	Purpura hemorrhagica
15	600,000		28	8,000	Purpura hemorrhagica
16	570,000	Toxin S C	29	64,000	Less severe
17	560,000	Toxin S C	30	100,000	Less severe
18	690,000		July—		
19	690,000		1	150,000	Well
20	930,000		2	250,000	Well
21	860,000	Animal Well	3	380,000	Well
22	970,000	Animal Well	4	460,000	Well
23	1,700,000	Animal Well	5	370,000	Well
24	1,040,000	Animal Well	6		Well
25	440,000	Animal Well	7	570,000	

disappeared as soon as the count rose. No tendency to bleed was observed in other animals treated with the same and much larger doses of diphtheria toxin. This, I think, was due to the fact that the platelet count did not fall to such a low level.

In order to prove that an absence of platelets is a cause of hemorrhagic disease, it would be desirable to find the agency through which this might be possible.

Morawitz<sup>25</sup> found that platelets contain large amounts of prothrombin (or thrombogen or the antecedent substance of the fibrin ferment). Jones,<sup>26</sup> working in Professor Howell's laboratory, confirmed the results of Morawitz, and in addition demonstrated that platelets liberate a throm-

<sup>25</sup> Morawitz Arch Klin Med, 1904, lxxiv, 215. Cited by Jones, Note 26.

<sup>26</sup> Jones, S Bayne. The Presence of Prothrombin and Thromboplastin in the Blood Platelets. Am Jour Physiol, 1912, xxx, No. 1.

boplastic substance which he named thromboplastin. These results make it appear remarkable that blood in which platelets can hardly be demonstrated is able to clot both quantitatively and at a normal rate. This is, however, beyond question a fact. Both Denys and Hayem thought so from their microscopic studies of blood films. My studies, which confirm their views, were as follows:

The platelet count in dogs was reduced to about 10 per cent of normal by repeated injections of benzol. In these cases blood coagulation was carefully studied. The fibrinogen content of the blood was shown to be at the upper limit of normal (0.55 per cent to 0.65 per cent). The coagulation time was normal or slightly prolonged. The latter was accounted for by the presence of jaundice. All the fibrinogen present was transformed into fibrin by coagulation—at least the blood-serum obtained, after coagulation, was shown to be free from fibrinogen (the serum, when neutralized and heated to 58 C, gave no precipitate). The results in the human cases were in harmony with the experimental. The coagulation time was about normal—in some cases even shorter than normal—the clot was firm and a microscopic study of the fibrin showed no striking qualitative or quantitative deviation from the normal.

The macroscopic appearance of the clot, noted both in the experimental and in the human cases, differed strikingly from that of normal blood, inasmuch as it failed to retract and extrude serum. Hayem,<sup>2</sup> the first to observe non-retractility of the blood-clot, performed some very interesting experiments which throw light on its meaning. He collected horse blood, and at a low temperature, threw down the red and white corpuscles by centrifugalization. The supernatant plasma contained an abundance of platelets. From a portion of this, platelets were removed by filtration. Both specimens were then allowed to clot. The portion containing platelets retracted and extruded serum. The filtered portion clotted, but failed to retract. Hayem concluded that platelets give to the clot its property of retractility. It has been observed, however, that under some conditions, blood containing an abundance of platelets, gives a non-retractile clot. The clinical and experimental results on this subject of Hayem, Le Sourde and Pagniez<sup>27</sup> and others, may be summarized by saying that the presence of blood-platelets seem indispensable for normal retractility of the blood-clot, but retraction occasionally fails to take place even when platelets are present in abundance.<sup>2, 27</sup> Le Sourde and Pagniez<sup>28</sup> have recently shown that the blood of patients with purpura hemorrhagica gives a retractile clot if a suspension of blood platelets

<sup>27</sup> Le Sourde and Pagniez. *Jour de physiol et path gén*, 1907, ix, No. 4.  
Cited by Pratt.

<sup>28</sup> Le Sourde and Pagniez. *Un cas de Purpura Hemorrhagique avec Disparition totale des Plaquettes du sang*. *Bull et mém Soc méd d hôp de Paris*, July 12, 1912.

is added to it. Whether this interesting but more or less an artificial phenomenon (failure of the clot to retract) is an evidence of an abnormal fibrin formation which could play a part in the pathogeny of hemorrhagic disease, is questionable. It may be due to the fact that platelets are not present to anchor together the filaments of fibrin, or it may be comparable to the failure of the milk clot to retract. This happens if rennet is added to it in insufficient amount.<sup>29</sup>

Hayem produced a condition of the blood which both Denys<sup>1</sup> and he<sup>3, 30</sup> considered analogous to purpura hemorrhagica. He injected blood-serum of one animal into the circulation of an animal of different species. The platelets began immediately to stick together and finally formed clumps so large that they were to a great extent filtered off from the circulating blood by the capillaries. He states that a similar condition follows the injection of rattlesnake venom in animals. This was considered by Denys and Hayem to be the pathogenesis of purpura hemorrhagica. They suggested that multiple platelet emboli could account for the purpura, and abnormal coagulation for the hemorrhage. This ingenious and attractive theory explains, perhaps, some types of hemorrhagic diathesis. I am, however, unable to reconcile it with all the data obtained in my studies and at present believe that the type of disease described in this paper has a totally different cause. It is not desirable at present to discuss this question at length, for experimental purpura hemorrhagica produced by the injection of diphtheria toxin offers such an admirable opportunity for further study. This condition we are safe in assuming is exactly the same as that observed in humans. It may be permissible, however, to mention briefly several observations which I cannot reconcile with the theory of Denys and Hayem.

1 Following the intravenous injection of peptone into animals, a condition results which is analogous to that produced by Hayem with animal serum. The platelets clump together and are to a large extent filtered off from the circulating blood. Such blood withdrawn in a blood-pipet and diluted (1-100) with Wright and Kinnicutt's solution or a 4 per cent aqueous solution of sodium metaphosphate, gives a striking picture. The red cells are laked and the platelets are clumped into masses of from several to several hundred. Such a condition as this was not observed in the study of my human or experimental cases. Even in Experiment 34, when 1,700,000 platelets per mm. of blood disappeared from the circulation within three days, no tendency to clumping was observed.

2 In Case 7 a petechial rash appeared immediately after straining at stool. This certainly suggests a wide-spread capillary rupture as the cause.

<sup>29</sup> R. Bräuler. Der Einfluss verschiedener Labmengen und verschiedener Temperaturen auf die Gerinnung der Milch und auf die mikroskopische Struktur der Kasein und Fibringerinnsel. Arch. f. ges. Phys., 1910, cxxiii, 519.

<sup>30</sup> Hayem, G. Leçons sur les maladies du sang. Masson, 1900, p. 586.

of purpura, not platelet emboli. Other facts might be mentioned in support of this. For instance, purpura was often brought out by blows, rubbing, etc. Petechias were most abundant on the dependent parts when the patients were up and about, and often disappeared completely when they were confined to bed.

3 In Case 4 the platelet count was below 10,000 for a period of nearly a month. During this time great numbers of petechias appeared, and at this time there were scarcely enough platelets present to produce a sufficient number of emboli to account for them.

4 In Case 1, the purpura faded rapidly after transfusion and did not reappear as the platelets introduced by transfusion vanished. If the disappearance of these platelets was the result of clumping and embolism, the purpura should have been increased instead of decreased by transfusion.

Hemorrhagic diathesis of this type can be accounted for theoretically best, I believe, as follows. It is well known that hemorrhage is not stopped by a clot, such as is seen on the surface of wounds, but chiefly by intravascular plugs (thrombi). A clot and a thrombus have totally different architectures and modes of formation. A clot is formed from blood at rest, and consists of a homogeneous mixture of platelets, red cells, leukocytes, fibrin, etc. Without question, the coagulation of fibrinogen plays the essential rôle in this process. It takes place at about the normal rate, and quantitatively whether platelets are present or not. A thrombus, however, is a different matter. It is formed from blood which is flowing, and we have reason to believe that for its formation a certain number of platelets is indispensable. Platelets, from the property they possess of sticking to injured tissue and then to each other, adhere to any injured point in a blood-vessel and are deposited there in enormous numbers by the blood as it flows past<sup>31</sup>. This is the beginning of the process which plugs a bleeding vessel. Later, fibrin, leukocytes and red cells are deposited and, finally, thrombosis is complete. Judging from the experimental results, platelets not only initiate, but also make up a large part of the bulk of a completed thrombus. It is easily conceivable that an almost complete absence of platelets from the blood should lead to abnormality in the initiation or completion of thrombosis, and be a cause of prolonged hemorrhage, whether the fibrin-forming elements were normal or not. The fact that a patient bleeds for an hour or more from a pin prick or a mere scratch is abundant evidence that in that patient thrombi fail to form, and since an absence of blood

31 Hayem, G. (a) *Recherches sur l'atomie norm et path du sang* Paris, 1878, (b) *Compt rend Acad des sc*, July 18, 1882, (c) Bizzozero *Virchows Arch f path Anat*, 1882, xc, 261. (4) Eberth and Schimmelbusch *Virchows Arch f path Anat*, 1885, ci, 1886, ciii, cv. The foregoing cited by Welch. (e) Welch, William H. *The Structure of White Thrombi* *Tr Path Soc Philadelphia*, 1887, xii.

platelets is constantly accompanied by this phenomenon, it seems evident that the rôle played by platelets in thrombus formation is an essential one. I have studied experimental thrombi by the methods used by Professor Welch in rabbits in which the platelet count was reduced to as low as 60,000 by subcutaneous injections of benzol. Thrombi formed in such animals. They seemed smaller than normal, but contained, as do normal thrombi, great numbers of agglutinated platelets and leukocytes, and also fibrin and red cells. These results harmonized with the fact that these particular animals displayed no striking tendency to bleed abnormally long. We have not yet studied thrombus formation in the more extreme cases in which platelets are almost totally absent from the blood and hemorrhage is excessive.

An absence of platelets perhaps accounts for the tendency to bleed from cuts. The explanation of the purpura, however, is not so clear. My evidence suggests that both forms of purpura (both the fine petechias and the ecchymoses) are due to hemorrhage from ruptured blood-vessels, and not to thrombosis nor platelet emboli. Whether or not the vessels in this disease are abnormally friable is difficult to say. It is possible that in healthy individuals, under the usual conditions of life, a few capillaries are continually rupturing, and that the minute ruptures are immediately closed by the adherence of a few platelets and a few filaments of fibrin. When the tendency to bleed is pathologically enormously increased, it is possible that such ruptures lead to visible hemorrhages which appear as fine petechias. Bruising, rubbing, etc., would cause a number of ruptures in a small area and lead to the formation of the larger hemorrhages — the ecchymoses. This explanation seems in accordance with facts as I now understand them. It explains, I believe, the fine petechias and the traumatic ecchymoses of the platelet free type of disease. It is not believed, however, that it would account for the larger purpuric flecks seen in other types of hemorrhagic disease, which appear without local causes.

As to etiology, it may be said that any agent which lowers the platelet count to a point of almost complete absence would appear to be a cause of purpura hemorrhagica. Purpura hemorrhagica of this type, would seem to be then, a symptom, not a disease. Severe cases have been observed complicating lymphocytic leukemia, hemorrhagic small-pox, tuberculosis, nephritis, aplastic anemia, benzol poisoning, diphtheria and gastro-intestinal conditions. Further study will undoubtedly add to this list. A minority of the cases develop in individuals who seem otherwise healthy.

#### SUMMARY AND CONCLUSIONS

- 1 By comparing symptoms and blood findings in all patients observed during a period of three years, who displayed a pathologic tendency to bleed, it has been possible to pick out a certain group of cases which



presents a characteristic clinical picture, which is due wholly or in part, it is believed, to an enormous reduction in the number of blood-platelets

The disease in its severer form almost constantly presents the following symptom-complex 1 Purpura of one or two types—petechias or ecchymoses 2 Hemorrhage from mucous membranes 3 A tendency to bleed from every vascular lesion, *no matter how produced* In consequence of this tendency, the bleeding time is very greatly prolonged, often exceeding two hours 4 A normal coagulation time 5 A firm blood-clot 6 In consequence of the absence of platelets, a clot which does not retract and extrude serum In all cases (seven) seen by me showing the above picture, the number of platelets was reduced almost to a point of absence Counts were all below 10,000, and as a rule, below 1,000 (The normal platelet count varies from 200,000 to 400,000 )

The disease in its milder form presents a different picture The most common symptoms in the milder cases are ecchymoses following slight injury and epistaxis Sometimes neither purpura nor bleeding from normal mucous membranes appears and the only evidence of hemorrhagic diathesis is severe hemorrhage accounted for to a greater or less extent by local causes, for example, continued bleeding from intestinal ulcers, from esophageal varices, profuse and prolonged menstruation, etc The bleeding time in the mild cases is sometimes normal and sometimes slightly or moderately prolonged The coagulation time is normal, the clot firm, retractility diminished The diagnosis rests on the finding of a reduced platelet count It varied, in my cases (six), from 20,000 to 65,000

2 Hemorrhagic diathesis can be followed best in this disease by determining the bleeding time at frequent intervals The simple observation of purpura, spontaneous hemorrhage, etc, may lead to false conclusions in regard to the general condition, for these symptoms are often due to general and local causes combined

3 When there was opportunity to make such observations it was noted that the disease appeared when the platelet count fell to an extremely low level, persisted so long as the count remained low and disappeared as soon as the count rose

4 The disease was relieved immediately in two cases by direct transfusion of blood The relief was coincident with an increase in the platelet count, evidently a direct result of the transfusion Symptoms returned when the platelet count fell again

5 The disease was produced in rabbits by reducing the platelet count with diphtheria toxin The disease appeared the day the platelet count descended to a point of almost complete absence and persisted until the platelet count rose Hemorrhagic diathesis in mild form was brought

about with repeated injections of benzol. In the latter experiments the count did not descend to such a low level as in the former.

6 In a series of thirty-eight animal experiments,<sup>32</sup> in which the platelet count was enormously changed with subcutaneous injections of benzol, diphtheria toxin and tuberculin, and also in a large series of cases in humans in which routine platelet counts were made, only those having extremely low counts gave the complete symptom-complex described above. Several platelet counts between 40,000 and 75,000 were observed in patients who had no marked tendency to bleed. This seems to be the level at which patients may or may not have an abnormal tendency to bleed. No counts lower than these were observed in patients not subject to hemorrhage.

7 The disease has been observed complicating a varied set of diseases — in severe form in lymphocytic leukemia, hemorrhagic small-pox, tuberculosis, nephritis, benzol poisoning, aplastic anemia and diphtheria. The one feature in common in these cases was the low platelet count and the modification of the clot dependent on it, i. e., absence of retractility. Purpura hemorrhagica of the type described would seem, therefore, a symptom, not a disease. It is caused apparently by any agent which reduces the platelet count to a sufficient degree.

In conclusion I wish to express my thanks to Drs. W. W. Gannett, F. C. Shattuck, F. T. Murphy and Hugh Cabot of the Massachusetts General Hospital, to Dr. L. A. Conner of the New York Hospital, to Privatdozenten von Jagie of the von Noorden clinic, Kren of the Riehl clinic and Schick of the Escherich clinic in Vienna, and to Professor von Romberg of the Medical clinic in Tübingen for the privileges granted in their wards and laboratories while this study was being completed, also to Drs. J. H. Wright and Roger Kinnicutt of the Massachusetts General Hospital for the use of their excellent method for counting platelets, and to Dr. G. H. Whipple of the Hunterian Laboratory for Experimental Pathology of the Johns Hopkins Hospital for the privilege of working in his laboratory and for suggestions regarding fibrinogen analysis.

Rialto Building

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32 Duke, W. W. Paper not yet published.

# THE WASSERMANN TEST IN THE TROPICS

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Probably every physician who performs the Wassermann test adopts certain minor variations in technic, which tend to make the test more satisfactory in his hands. It is always interesting and instructive to learn the writer's technic before reading his results. The Noguchi modification<sup>1</sup> of the test has been used in the board of health laboratory at Ancon because it is one of the most accurate complement deviation tests for syphilis, because every reagent may be titrated separately and standardized, and because there is always abundant opportunity for obtaining human blood.

## TECHNIC

*Corpuscle Suspension*—A little over 1 cc of human blood is taken in 9 cc of a solution containing 0.9 per cent salt and 1.5 per cent sodium citrate. The corpuscles are washed three times with normal salt solution and then centrifugalized for measurement. As 1 cc of blood contains approximately 0.4 cc of corpuscles, the blood is taken into a graduated centrifuge tube and after washing, 0.4 cc of corpuscles are suspended in 10 cc of normal salt solution to obtain a 10 per cent suspension. This method of measurement is easy and gives a constant suspension.

*Hemolytic Amboceptor*—The amboceptor is prepared in the manner advocated by Noguchi. The amboceptor unit determined by the use of an overwhelming amount of complement has not been a satisfactory unit for practical purposes in my hands. Instead I have determined the amboceptor unit by the following method described by Noguchi. To a series of tubes each containing 1 cc of a 1 per cent suspension of human corpuscles and 0.02 cc of mixed guinea-pig serum is added a varying amount of amboceptor, the amount which causes complete hemolysis in two hours is considered one unit.

*Complement*—The complement consists of the mixed sera from several guinea-pigs. This is never over twenty-four hours old at the time of use. The blood is obtained by aspirating the heart under aseptic precautions with a 10 cc Luer syringe. An anesthetic is always employed. The same pigs are used repeatedly. There are twelve small pens set aside for the "Wassermann" pigs, the test is performed twice a week, thus each pig is bled about once every six weeks. The entire lot is changed about once in six months. The relative amount of complement in the serum does not seem to be affected by bleedings of this frequency. The amount of complement required with one unit of amboceptor to cause complete hemolysis of 1 cc of a 1 per cent suspension of corpuscles is considered one unit. The test is performed with two units of amboceptor and two units of complement. For over a year a preliminary titration of the complement, as recommended by Craig,<sup>2</sup> has been made before performing the test.

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\*Manuscript submitted for publication July 18, 1912

1 Noguchi, H. Serum Diagnosis of Syphilis. J B Lippincott, Phila., 1910

2 Craig, Charles F. Further Observations on the Complement Fixation Test in the Diagnosis of Lues in the Military Service. Jour Infect Dis, 1911, 14, 216



isolated, 0.20 c c of whose serum would completely hemolyze 1 c c of a 1 per cent suspension of human red blood corpuscles

That these sera contained a true thermostabile antihuman hemolysin or amboceptor may be readily seen by Tables 1 and 2

These pigs had been living in the laboratory court-yard for several generations — about four years — and had been fed on a diet consisting exclusively of tropical grasses

The sera of another lot of guinea-pigs which had been on the isthmus but a short time was similarly tested. The sera from these pigs in most instances had no effect on human red blood corpuscles even if mixed in equal volumes, and in no instance was hemolysis seen with the use of less than 0.30 c c of serum to 1 c c of a 1 per cent corpuscle suspension

Since this episode we have run a control test tube with each pig's serum before mixing their sera for use in the test. This tube contains 1 c c of a 1 per cent suspension of red blood corpuscles and 0.20 c c of the guinea-pig's serum. It is incubated for one hour at 37° C, usually from 4 to 5 p. m., and then allowed to stand at room temperature overnight. This test has more than once justified its adoption as a routine procedure

#### MALARIA

Were malarial fever, malarial infection or relative malarial immunity to give a positive Wassermann test, or to interfere with any of the reactions taking place in the complement deviation test for syphilis, it would most seriously lessen the value of the test in the tropics or other malarial regions

TABLE 3—RELATION OF MALARIA AND THE WASSERMANN REACTION

Patients infected with malarial parasites on the day of admission and having blood taken for Wassermann on the same day	15
Wassermann tests negative	12
Wassermann tests positive	3

These three positive cases were as follows

Periostitis of tibia	1
Syphilitic arthritis	1
Good history of syphilis	1

Of these fifteen infections there were twelve æstivo autumnal and three of the tertian form

TABLE 4—RELATION OF MALARIA AND THE WASSERMANN REACTION

Patients infected with malarial parasites on the day of admission and having blood taken for Wassermann in from one to four days later	84
Wassermann tests negative	68
Wassermann tests positive	16

Of these sixteen positives there were

Typical secondaries	5
Others with characteristic or suspicious lesions	8
Insufficient data	3

Of these eighty-four there were 69 E. A., 2 E. A. and tertian, 9 tertian, and 4 quartan

TABLE 5—RELATION OF MALARIA AND THE WASSERMANN REACTION

Patients infected with malarial parasites on the day of admission and having blood taken for Wassermann on average of five to ten days later	65
Wassermann tests negative	47
Wassermann tests positive	18

Of these eighteen positives there were

Typical secondaries	2
Others with characteristic or suspicious lesions	12
Insufficient data	4

Of these sixty-five there were 56 E A, 1 E A and tertian, and 8 tertian

TABLE 6—RECAPITULATION AS TO MALARIA AND THE WASSERMANN REACTION

Wassermann tests on cases of malaria	164
Wassermann tests negative	127
Wassermann tests positive	37

Of these thirty-seven positives, thirty were clinically considered complicated with syphilis

During the dry season in the Canal Zone 10 per cent of the laborers at work and without symptoms, and 30 per cent of their families, were found by Dr S T Darling<sup>3</sup> to be infected with malarial parasites. If this number can be demonstrated undoubtedly a much greater number are carrying malarial parasites, their antibodies or both.

One hundred and sixty-four cases of the 2846 here considered exhibited malarial parasites at some time during the admission period in which their blood was taken for the Wassermann test. These cases covered a period of nineteen months. Thirty-seven of these 164 gave positive reactions. The great majority of the thirty-seven showed indisputable evidences of syphilis, or gave histories or presented lesions which rendered a diagnosis of past syphilitic infection highly probable. In seven I was unable to collect satisfactory data in reviewing the cases. Many of those giving negative reactions presented nothing in histories or physical signs directly suggestive of syphilis, and a few were purposely taken as controls.

#### LEPROSY

The Wassermann test was performed on forty-two cases of leprosy, sixteen, or 38 per cent, gave strong positive reactions, and four others gave weak positives, making a total of 47 per cent positive. All of these were clinically well marked cases, some very much advanced. Some of the most advanced cases gave negative reactions. Whether any of these cases were complicated with syphilis or not we had no means of deter-

<sup>3</sup>—Darling, S T. Transmission of Malarial Fever in the Canal Zone by Anopheles Mosquitoes. Jour Am Med Assn, 1909, lxx, 2051.

mining, for the leprous lesions were such as to obscure a clinical diagnosis of syphilis and such histories as could be obtained were of but little value. Probably a similar condition exists in most leproseria, and if such is the case the influence of uncomplicated leprosy on the Wassermann reaction is a problem which remains to be solved.

Twelve of our forty-two patients were under 20 years of age. Nine of these gave negative reactions, two gave weakly positive reactions and one gave a strongly positive reaction.

Since performing these tests Noguchi's article entitled "Experimental Research in Syphilis"<sup>4</sup> has appeared, and in this article he states that the serum from each of three lepers gave a negative reaction when a culture of *Treponema pallidum* was used as antigen.

When opportunity is afforded, the forty-two cases above cited will be again tested using the two types of antigen simultaneously.

#### YELLOW FEVER

The test was performed with the serum of one patient who had had yellow fever and with the serum of one during the attack. Both tests were negative. The latter was seen at the Culebra Island Quarantine Station on about the sixth day of the disease. His temperature had just dropped to 98.6 F, his pulse was 40. There was an icteric tint to the skin. His urine was brownish-yellow and became solid on boiling. The patient was intelligent and gave a straight-forward history admitting gonorrhea and denying syphilis. There was no evidence of either past or present syphilitic infection. The serum separated from the clot without any hemolysis taking place and was mahogany brown in color. The Noguchi test was performed with 0.02 c.c. of active serum, with 0.08 c.c. of inactivated serum, and with 0.16 c.c. of inactivated serum. There was no inhibition of hemolysis in any instance.

On account of its possible bearing in this connection I wish to allude to the effect of bile or bile constituents on the reaction. It has been stated that if they be present in a blood-serum, such serum will give a positive reaction even though syphilis may be absolutely excluded, and that if bile be added to a normal serum it will also give a positive reaction.<sup>5</sup> (It must be borne in mind that these statements referred to the original Wassermann test while this paper deals with the Noguchi modification only.) It was possible to confirm this latter statement in a

4 Noguchi, H. Experimental Research in Syphilis. Jour. Am. Med. Assn., 1912, LVIII, 1163.

5 Kaplan, D. M. The Theoretical Consideration of the Wassermann Reaction and its Practical Application. Am. Jour. Med. Sc., July, 1910.

measure by the addition of varying amounts of highly diluted bile to normal serum. However, the results obtained with naturally jaundiced sera were satisfactory.

In the series of tests considered in this paper the sera were moderately or deeply jaundiced in ten instances. Nine of these sera gave negative reactions. Hemolysis took place as quickly and was as complete with these sera as with other normal sera which were examined at the same time. The jaundiced serum which gave a positive reaction did not inhibit hemolysis in the control tube, a phenomenon which may occur when bile is added to normal serum.

#### BLACKWATER FEVER

Blackwater fever causes a hematogenous jaundice and the blood serum is mahogany-brown in color. Each of four cases gave a negative Wassermann test.

#### YAWS

Two cases of yaws in each of which *Treponema pertenue* was demonstrated and in which there was no history of syphilis and no lesions resembling syphilids other than the typical yaw rupia and the general glandular enlargement, gave positive reactions. A third and similar case gave a negative reaction on two occasions.

#### FILARIASIS

The reactions in the two cases of filariasis (*F. bancrofti*) of long standing were negative. Both of these patients exhibited filarial embryos in the blood-stream at night and both passed chylous urine containing the filarial embryos. The second patient, a white man, claims that he was treated for the same condition in British Guiana in 1904.

#### AMEBIC DYSENTERY

Five cases of amebic dysentery gave negative reactions. Four of these cases were due to *Entamoeba histolytica*, and one had a heavy infection of *Entamoeba tetragena*.

#### ARTHRITIS

Tertiary syphilis is seldom held responsible for joint lesions by clinicians.

If a positive Wassermann test coupled with a positive therapeutic test may be taken as a criterion of diagnosis, syphilis plays a most important part in the causation of arthritis.

More than 40 per cent of the cases of arthritis on which Wassermann reactions were requested during the past eighteen months have given positive tests. This percentage would be still higher if those cases in which a tentative diagnosis of gonorrheal arthritis might have been made were excluded.



The arthritides were characterized by the cardinal signs of inflammation, heat, pain, aggravated by motion or pressure, and swelling. Many of these joints were simply boggy, some had effusion. These lesions were almost always multiple.

The physicians in the medical wards of Ancon Hospital requested the Wassermann test on this class of cases, and to them belongs the credit for suspecting the possibility of syphilis. I present them here to call attention to the value of the test in cases of arthritis.

Out of 100 cases of arthritis, some without other discernible lesions of syphilis and some with one or more tertiary manifestations of the disease, all secondary stage cases being excluded, forty-one, or 41 per cent, gave positive Wassermann reactions.

In a recent number of *Deutsche medizinische Wochenschrift*, Bering<sup>6</sup> describes a series of eleven cases of arthritis, seven of them not presenting any lesion of syphilis other than the joint lesions, and ten of them giving positive Wassermann reactions.

#### AUTOPSIES

The Wassermann test is a reaction of value in a certain number of cases which come to the post-mortem table. As time goes on, its value will probably become more and more appreciated. If the blood is recovered shortly after death it is apparently as serviceable as if obtained during life. If post-mortem changes have occurred there is an inhibition of hemolysis in the control tube. Swift<sup>7</sup> compared the Wassermann test and the Noguchi modification of the same with blood from autopsies in 1909, and a limited use of the test has been made since then.

Below are given some of our cases tested and the results of the tests.

Autopsy 2878	Man, aneurysm ruptured into pericardium, positive
Autopsy 2991	Man, gumma (?) of heart, positive
Autopsy 2994	Woman, extensive carcinomatosis, negative
Autopsy 3030	Man, myocarditis, negative
Autopsy 3032	Man, aneurysm, ruptured, positive
Autopsy 3046	Child, malaria, lymphatism, negative

#### CONCLUSIONS

1 Guinea-pig serum must be tested for native antihuman hemolysin in certain localities and all sera in which they are found discarded.

2 Malarial infection does not affect the Wassermann reaction (Noguchi modification).

3 Our cases of filariasis, yellow fever, blackwater fever and amebic dysentery all gave negative reactions. Their number is too small to draw conclusions from.

<sup>6</sup> Bering, F. Acquired Syphilitic Joint Disease. *Deutsch med Wchnschr*, 1912, xxxviii, 393.

<sup>7</sup> Swift, Homer F. A Comparative Study of Serum Diagnosis in Syphilis. *THE ARCHIVES INT MED*, 1909, iv, 377.

4 Two out of three uncomplicated cases of jaws gave positive reactions

5 The Wassermann test is of great value in cases of arthritis of uncertain etiology

6 The Wassermann test should be made an aid to the pathologist in a considerable number of autopsies

I here wish to express thanks to Col John L Phillips U S A Acting Chief Sanitary Officer, Isthmian Canal Commission, for permission to publish this paper

I also wish to express thanks to Dr S T Darling Chief of Laboratory, Ancon Hospital, for helpful suggestions given during preparation of this paper

## POISONING BY NITRIC OXID FUMES

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This case of fatal poisoning by nitrogen tetroxid fumes is reported for its medicolegal interest and also because of the rarity of the condition and a general lack of recognition of the pathological changes in the lungs of persons dying from the action of this very dangerous gas

When nitric acid acts on certain metals, such as copper, silver, or cadmium, a gas is given off with the composition of NO or nitrogen dioxide. When this gas comes in contact with the air it absorbs oxygen, with the production of nitrogen tetroxid or  $N_2O_4$ . If either of these compounds of nitrogen and oxygen comes in contact with moisture, nitrogen dioxide forms nitric acid, while nitrogen tetroxid is slowly decomposed into nitric and nitrous acids. These are the decompositions which occur when brown fumes are given off by the action of nitric acid on the substances mentioned above.

When strong nitric acid acts on organic bodies it produces nitrogen tetroxid. This immediately decomposes, however, into a mixture of nitrogen dioxide and nitrogen tetroxid. The nitrogen dioxide is continuously converted into nitrogen tetroxid by the action of the atmospheric air. Inhalation of these gaseous compounds occasionally occurs in laboratories or factories where considerable quantities of these fumes are formed, either during the course of some reaction or when a carboy of nitric acid is spilled.

The inhalation of nitrogen tetroxid vapor, if not too concentrated, causes at first no symptoms, with the exception of a slight tendency to cough and an acid taste in the mouth. It has occasionally been observed that workmen have remained for some hours in a room in which nitric acid has been spilled without showing any evidences of injury, or that if on feeling uncomfortable they went into the open air, the symptoms have disappeared rapidly only to recur in full force six to eight hours later. If the vapors are concentrated, the patient may suffer immediately from severe dyspnea, a feeling of pressure on the chest, coughing, faintness and cyanosis. Dyspnea and slight cyanosis are the frequent symptoms, the patient often on reaching the air also vomits any food that may be in the stomach and then feels perfectly well for a period of six or eight hours. At the end of this time often without any inciting cause some-

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\* Manuscript submitted for publication Aug. 31, 1912.



In patients who have inhaled small amounts of gas and have improved after the first attack of edema of the lungs, the disease may continue for a number of days with the clinical symptoms of acute bronchitis and evidences in the chest of lobular or lobal pneumonia. Usually there is extreme dyspnea. The sputum is tenacious, yellowish or brown. Vomiting may be so extreme as to mask the pulmonary symptoms, though as a rule this is uncommon. Such cases may recover, but often show an increased liability to bronchitis or pneumonia for months afterward.

At autopsy the larynx, trachea and bronchi are congested and of a reddish or brownish color. If the patient dies shortly after exposure, the

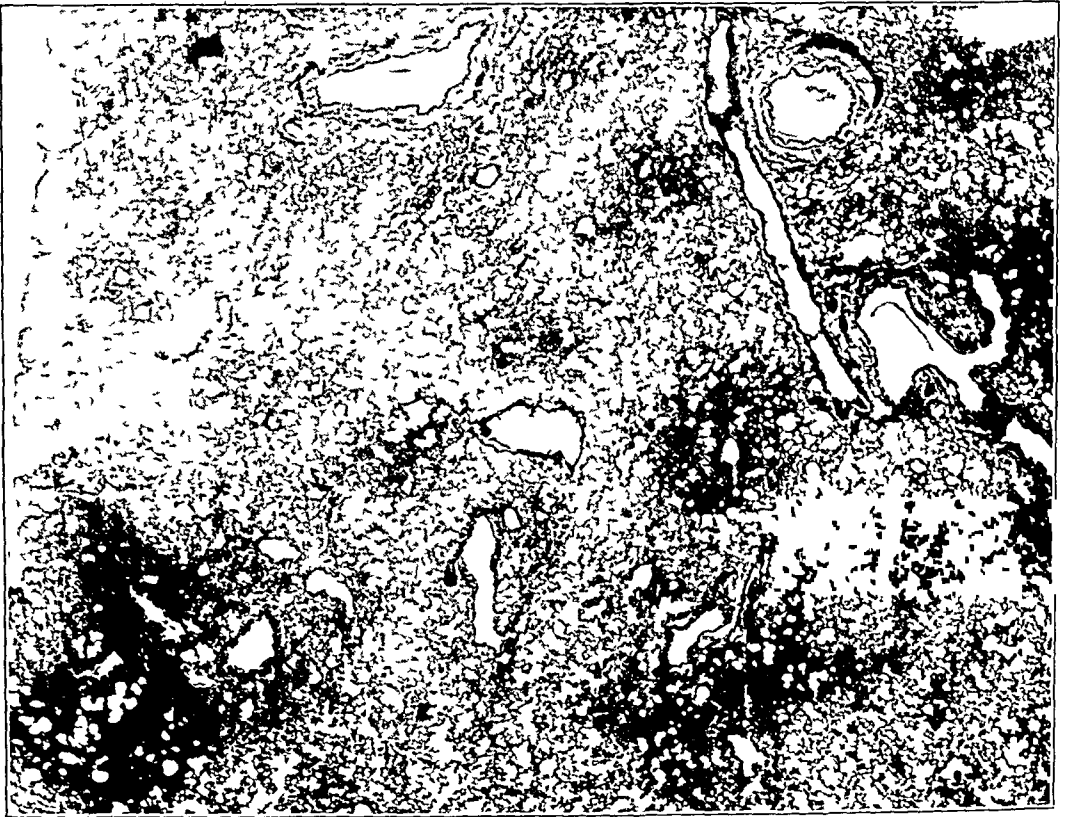


Fig 2—Dog 4 Lobular pneumonia with emphysema five days after inhalation of gas. Low power.

lung is edematous, in those living for several days, it is emphysematous, with, in addition a moderate amount of pneumonic exudate. The vessels of the lung often contain thrombi. From the cut surface exudes a reddish or brownish fluid. In the other organs ecchymoses are occasionally found. Focal necroses may occur in the liver. The meninges are often congested and there are occasionally punctate hemorrhages throughout the substance of the brain. The kidneys have in a few cases shown acute degeneration or acute nephritis, generally, however, they are not much altered.

The number of published cases of death following the inhalation of vapors of nitrogen tetroxide is not very large but owing to the greatly increased use of nitric acid in the arts, cases of such poisoning are likely to be more frequent in the future, and they may also assume a medico-legal importance in connection with accident insurance and employers' liability acts. On this account the following fatal case is reported together with the results of animal experiments and a survey of the cases already published.

#### CASE REPORT

*History*—The patient D in this instance accidentally inhaled the fumes arising from a large vessel containing considerable quantities of nitric acid and a cadmium silver alloy. The room in which the experiment was conducted was small, and the patient experienced some discomfort and a sensation of choking and went into the open air. After a few minutes he vomited and then felt much better. There were no further symptoms until some six or eight hours later when he was seized with intense dyspnea and collapsed. Twenty-four hours later he entered the hospital, remaining there until his death seven days after the exposure.

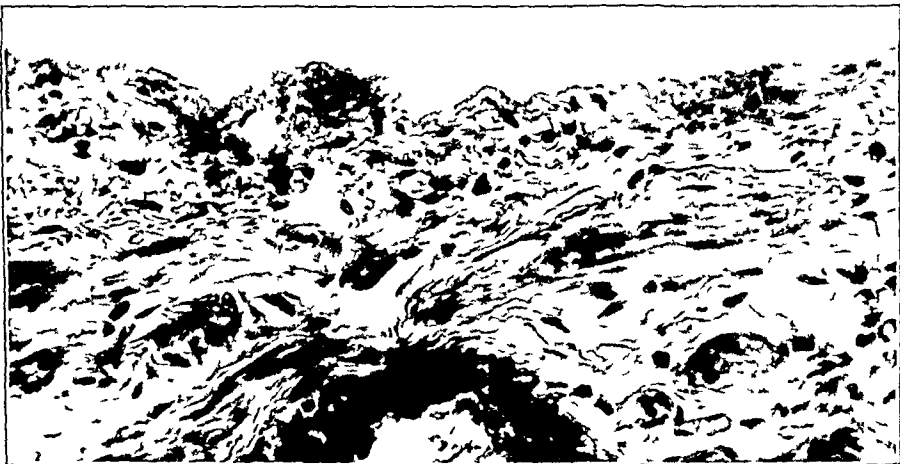


Fig. 3—Case D. Medium sized bronchus showing edema of wall and loss of epithelium.  $\times 250$

On admission he complained chiefly of weakness, pain in the throat and chest, and intense dyspnea.

*Examination*—Examination showed a well nourished man with slightly dilated heart of rapid feeble action, soft pulse. He was suffering at the time of the examination from very severe dyspnea with extremely rapid shallow respiration and marked cyanosis. Prostration was very extreme but the patient's mind was clear. The pupils were equal and reacted. The lips and tongue were intensely cyanosed, the throat was congested. The lungs showed marked dulness at both bases posteriorly, bronchovesicular breathing with slightly bronchial voice and scattered rales, most marked over the right base. The extremities were cold and cyanotic. The temperature ranged from 100° to 102° F., the pulse from about 100 to 140, respirations from 44 to 60 during the patient's stay in the hospital. He was given oxygen inhalations and blood was drawn for examination. It was very dark in color but when examined spectroscopically showed oxyhemoglobin only and no evidence of carbon monoxide<sup>2</sup> or methemoglobin. Under the stimuli-

<sup>2</sup> Illuminating gas poisoning had been suspected.

tion of the oxygen inhalations the patient got along fairly satisfactorily for several days. Examination of the urine showed Specific gravity, 1.026, albumin, 2 per cent by volume, a few leukocytes, mucus, and red cells, no casts. Repeated examinations gave the same findings except that three days before death the urine contained a trace of albumin only and a few hyaline casts. The day before the patient died there was 5 per cent of albumin by volume, with a few hyaline and granular casts.

During the last few days the patient's respiration was very labored, he was restless and complained of headache and nausea and was able to sleep only a few hours during the night. The day before he died he became very restless and was irrational, the pulse was very feeble and irregular, and breathing was increasingly difficult. While there was at times an annoying cough this was never a prominent symptom. The only alteration in the physical signs noted

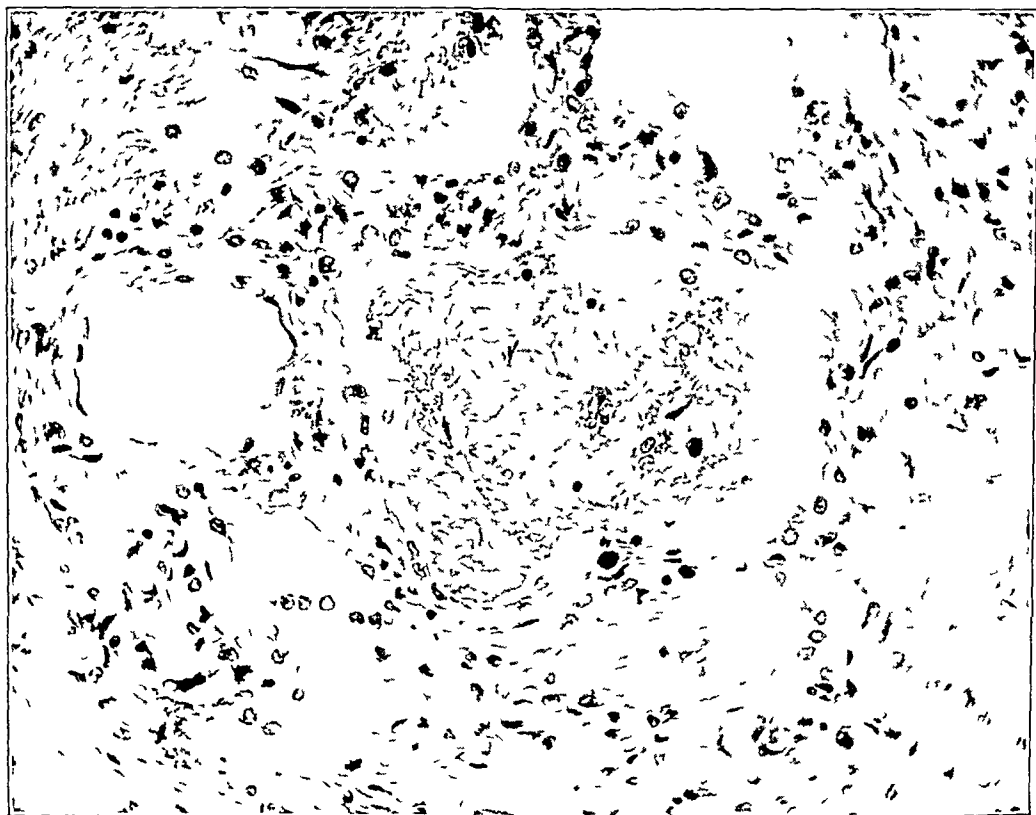


Fig. 4—Case D. Fibrous and hyaline exudate.  $\times 250$

was an increase in the area of dullness in the lungs and evidences of congestion and edema of the upper lobes.

The red blood cell count was 5,400,000 with normal morphology; the hemoglobin was 90 per cent. The white blood cell count was 17,000, polymorphonuclears 68 per cent, lymphocytes 30 per cent, basophils 2 per cent.

**Necropsy**—At autopsy, which was done after embalming with a fluid containing formaldehyd, the important gross lesions found were as follows:

1. An irregular cavity with sharply defined walls in the corpus striatum on each side of the brain containing a clear, colorless fluid.

2. A moderately dense lobular pneumonia in the lower and posterior portion of the lungs on both sides.

The liver and kidneys showed nothing abnormal. The heart was dilated and looked pale and fatty.

*Microscopical Examination*—The microscopical examination of the tissues was not at all interfered with by the previous embalming the organs being in excellent condition and thoroughly hardened.

The lesion in the brain was of especial interest inasmuch as the patient had had a severe accident about a year before his death. Yet the examination of the tissues involved did not permit of a connection between this lesion and the accident for the following reasons. First, the cavity contained clear watery fluid, which was not blood stained. Such a fluid would be seen only in either a congenital or a parasitic cyst of the brain and such a lesion would not in all probability be symmetrical. Second, the walls of the cavity were perfectly sharp. Microscopical sections showed that the individual brain cells along the walls were perfectly preserved, and that small capillary vessels had been torn across the ends still remaining open. There was not the slightest evidence of an inflammatory reaction or the formation of a membrane. It is probable therefore that this tear was formed post mortem by the injection at high pressure of the

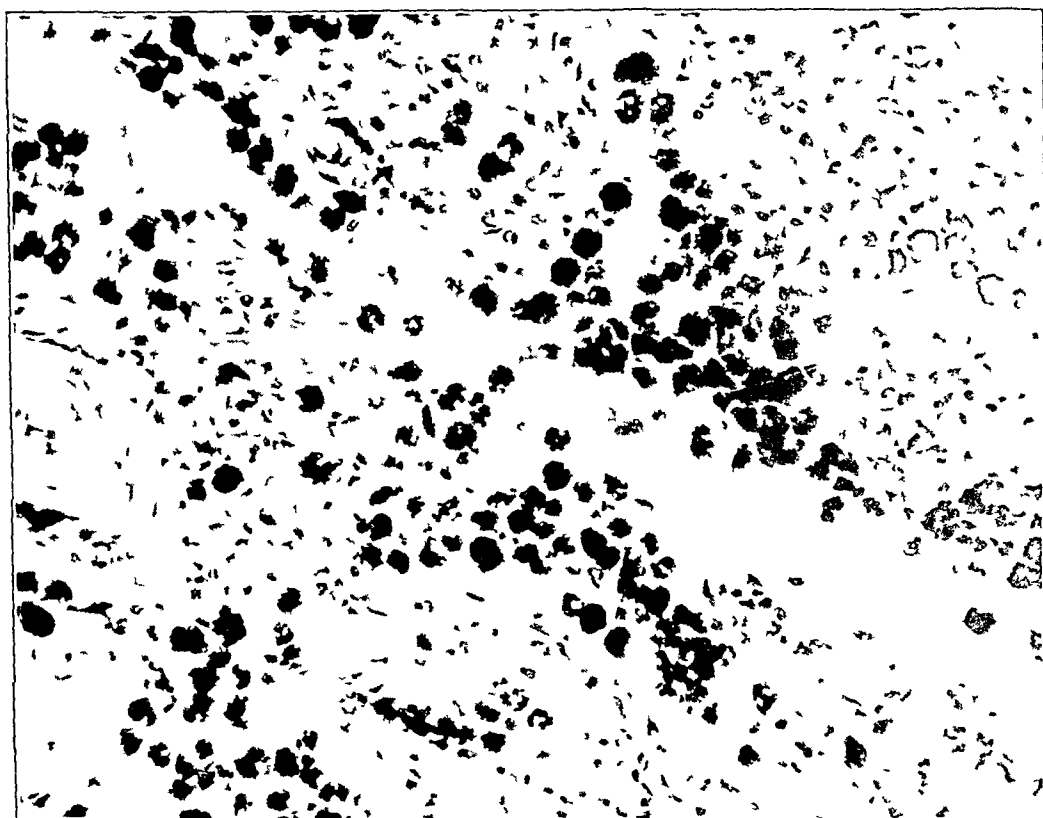


Fig. 5—Case D. Areas containing chiefly pigmented cells.  $\times 250$

embalming fluid. That this is possible was proved by some experiments on human cadavers in which similar artefacts were induced. The vessels may have been weakened by the action of the poison especially as Tomellini<sup>3</sup> has shown that in acute nitrite poisoning small hemorrhages can be found in the organs usually confined however to the stomach, intestine and liver. As stated above small quantities of nitrous acid may be formed when nitrogen tetroxide comes in contact with moisture. Such nitrous acid would naturally combine with the free alkali in the tissues and blood and circulate as sodium nitrite. This might be the cause also of the very soft and rapid pulse occasionally seen in these cases of poisoning and suggests an explanation for the very dark color of the blood noted in almost all cases of this form of intoxication it being well known that nitrites

<sup>3</sup> Tomellini, *Berlin path. Anat.* (Ziegler's) 1905 xxxviii 395



form methemoglobin on contact with blood. The amount, however, is as previously stated usually too small to give a characteristic spectrum.

The liver and kidneys showed practically no changes on microscopic examination. A large number of sections from the liver showed a very few small necroses and a little fatty degeneration. The kidneys also were in good condition with only a slight cloudy swelling of the tubular epithelium and some congestion of the tufts in the capsules and of the intertubular vessels, but there were no casts in the tubules and no evidences of interstitial nephritis.

The heart muscle showed a small amount of fat infiltration, but was otherwise normal.

The interesting lesions were those in the lungs. As stated above, there was a lobular pneumonia chiefly in the lower lobes. Between the areas of consolidation there was a very marked emphysema with absorption of a large number

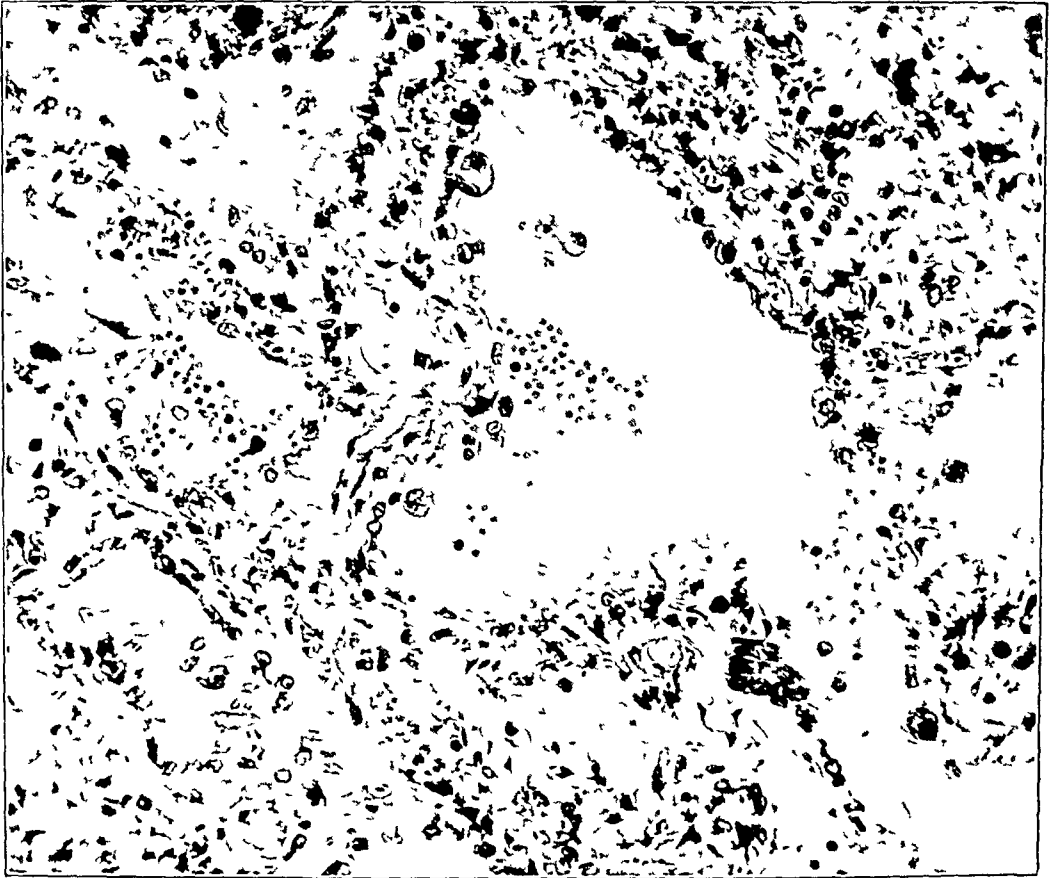


Fig 6—Case D Hemorrhagic portion of lung  $\times 250$

of alveoli so as to form large cavities easily visible to the naked eye a phenomenon which regularly occurs not only in human beings but also in experimental animals (Figs 1 and 2). The mucous membrane of the trachea and bronchi was desquamated over extensive areas (Fig 3). In some places fragments of the epithelial lining could be found still adhering to the walls or collected in masses in the lumen with extreme edema of the subepithelial connective tissue. Occasionally a bronchus was found into which had grown a cellular plug largely filling the lumen. About the smaller bronchi were areas of consolidation, the alveoli being filled either with a transparent albuminous mass or with fibrin containing a few leukocytes or with desquamated alveolar epithelium (Fig 4). In some places the epithelium was full of phagocytosed blood pigment (Fig 5).

Throughout, many alveoli contained red blood corpuscles (Fig 6) The capillaries in the walls were distended with blood and the walls themselves were very edematous and much thickened In places there was evidence of beginning regeneration of the alveolar epithelium which either lined the alveolus (Fig 7) in the form of a thin flat layer of cells much more prominent than is seen in a normal lung or occurred as swollen prominent hemispherical cells protruding into the lumen Sometimes these cells formed considerable masses or were fused into syncytial bodies (Fig 8) A true organizing pneumonia could hardly be said to be present The fibrous plugs occasionally became very dense and were covered with new epithelium, and in rare instances were penetrated by fibroblasts, but this was not at all a predominant lesion In other portions of the lung the alveolar structure had entirely disappeared, the lung being quite collapsed and the regenerating epithelium showing as solid syncytial masses or as strands of cells lying in the fairly dense pulmonary tissue (Fig 9) The upper portions of the lungs were fairly well aerated and showed a moderate emphysema but no

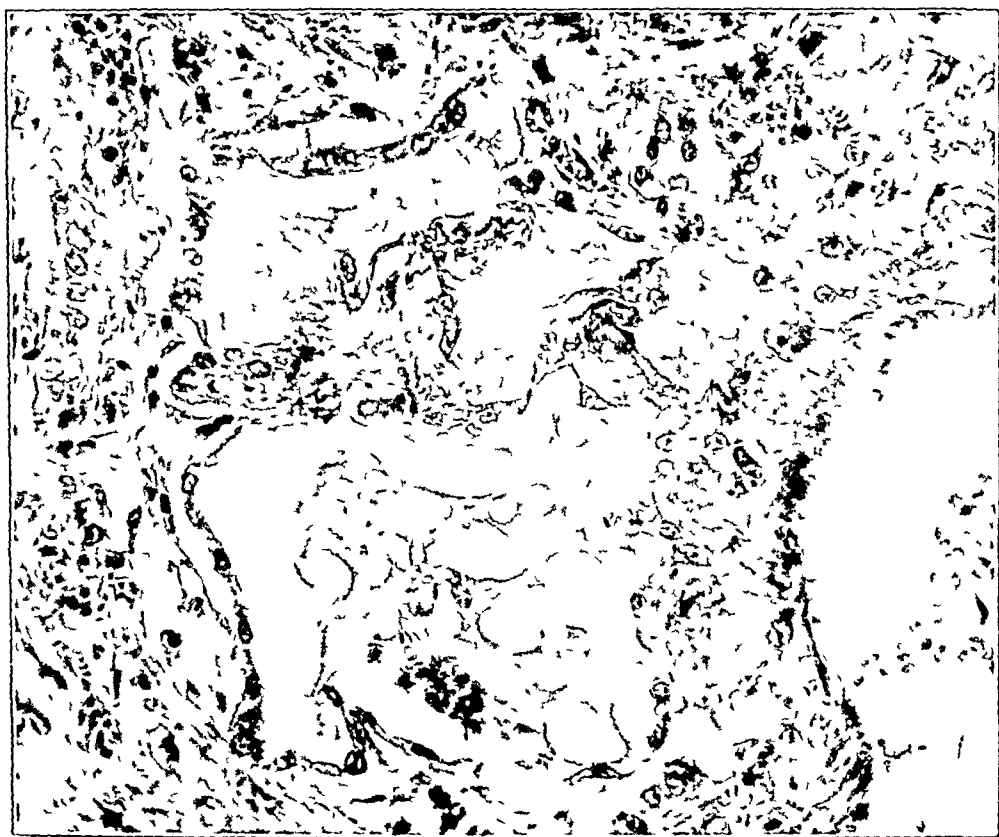


Fig 7—Case D Regeneration of alveolar epithelium  $\times 250$

other lesions The bronchial lymph-nodes were edematous and heavily pigmented, but otherwise normal In the smaller vessels of the lungs there were a number of parietal thrombi occasionally a thrombus filled the entire vessel and there was some proliferation of the endothelial lining showing that these thrombi were undoubtedly ante mortem Similar thromboses can be easily induced in animals by the inhalation of nitrogen tetroxid fumes Obviously no cultures could be made from the lung but a large series of sections were stained by the various methods used for detecting bacteria and no organisms could be found The condition was evidently a non progressive pneumonia due to irritation of the corrosive gases inhaled and showing a tendency toward repair

The history and clinical symptoms of the case and the nature of the lesions which correspond exactly with those described in other cases of nitrogen tetroxid

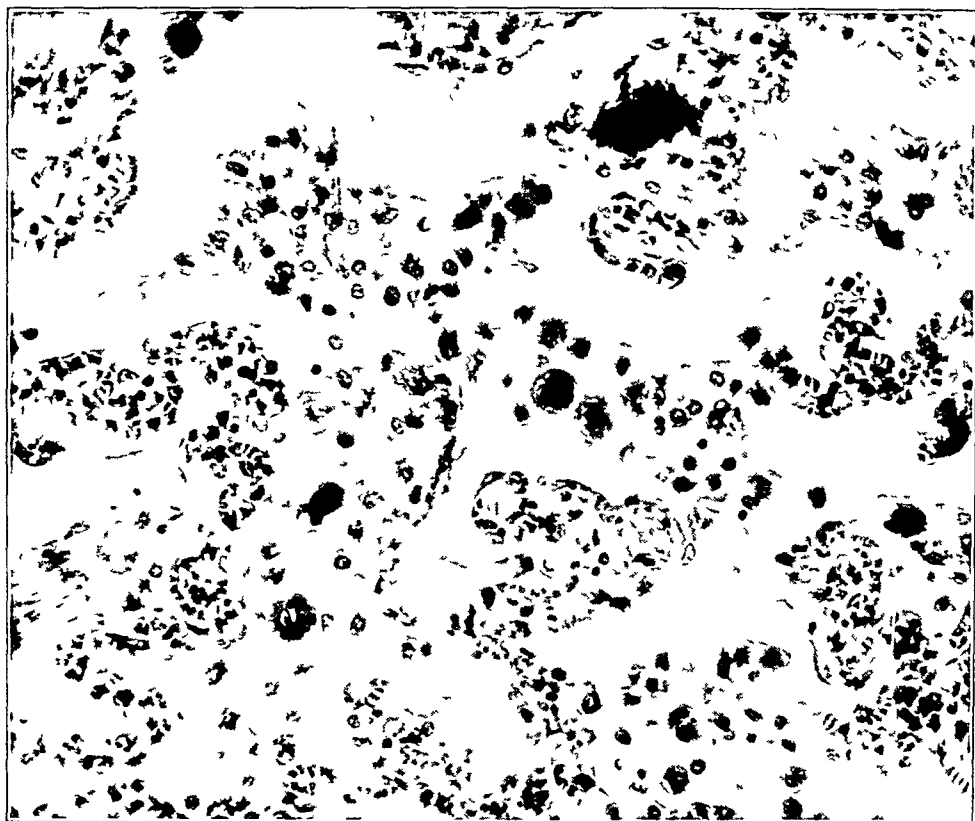


Fig 8—Case D Cellular exudate  $\times 250$

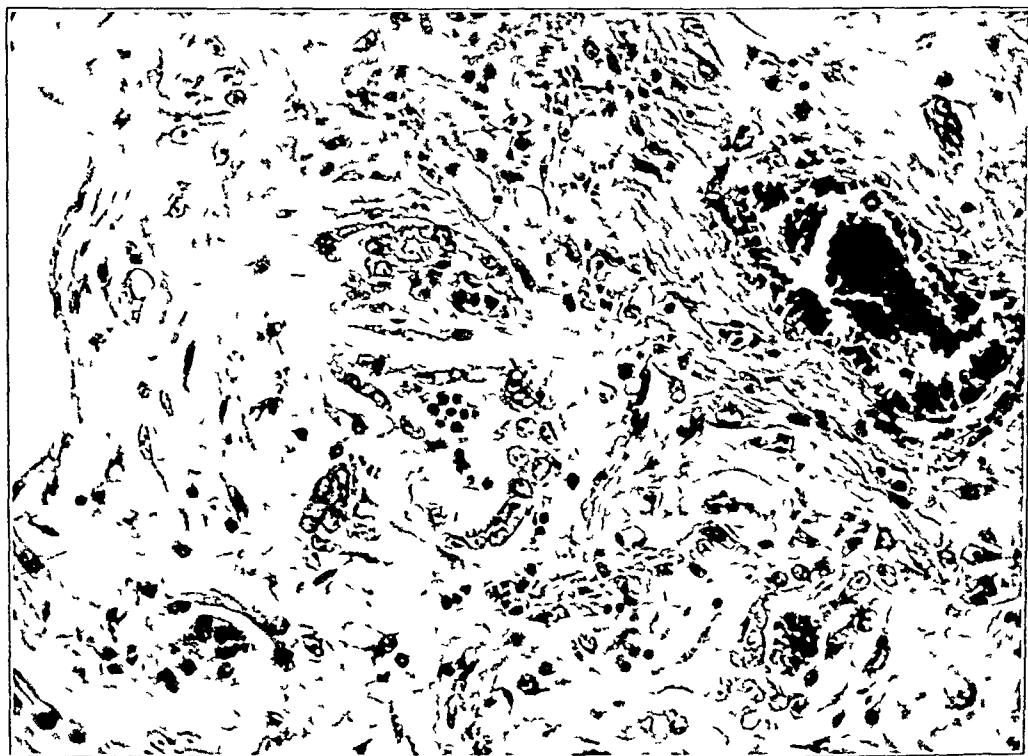


Fig 9—Case D Collapsed and edematous lung with new growth of alveolar epithelium and connective tissues  $\times 250$

poisoning and the confirmatory results of animal experimentation which follow point it seems to me to the conclusion that death in this case was unquestionably due to the accidental inhalation of this gas.

#### CASES FROM THE LITERATURE

An examination of the literature of nitrogen tetroxid poisoning shows only a moderate number of carefully studied cases. Most of the earlier ones were insufficiently examined and in few are there any microscopical reports.

Schubert, in 1911 was able to collect 213 cases of poisoning by nitrogen tetroxid, of which fifty-five were fatal. With very few excep-



Fig. 10—Dog 4. Bronchus showing epithelium and cilia still remaining but marked edema and congestion of submucosa.  $\times 300$

tions all these cases occurred in the last fifteen years and chiefly in the German Empire. There are no doubt many cases which have never been published for obvious reasons. Concentrated nitric acid is extensively used in the manufacture of gun-cotton, nitroglycerin, smokeless powder and celluloid, and it is said that many cases of poisoning occur in these factories. The following reports include only those in which an autopsy was performed.

The most carefully studied cases are the four which were reported from Cologne following the breaking of some carboys of nitric acid in a

small room about 12x6x8 feet. The clinical histories were reported by Savels,<sup>4</sup> the pathological findings by Loeschke,<sup>5</sup> and the medicolegal aspects of the cases by Czaplewski<sup>6</sup> and Schubert.<sup>7</sup> While the reports do not wholly agree in minor details, the important findings are given so fully that a very satisfactory picture of poisoning of this type is presented. For this reason a full abstract of these cases is given here.

**CASE 1—B. K.** The patient was a man, 42 years old. He was cleaning out the room after the accident and remained in it for about twenty minutes, when he felt weak and went home. He vomited and had diarrhea, and some hours after the accident was seized with intense dyspnea, cyanosis, and cardiac weakness. He died in the hospital about five and a half hours after he had

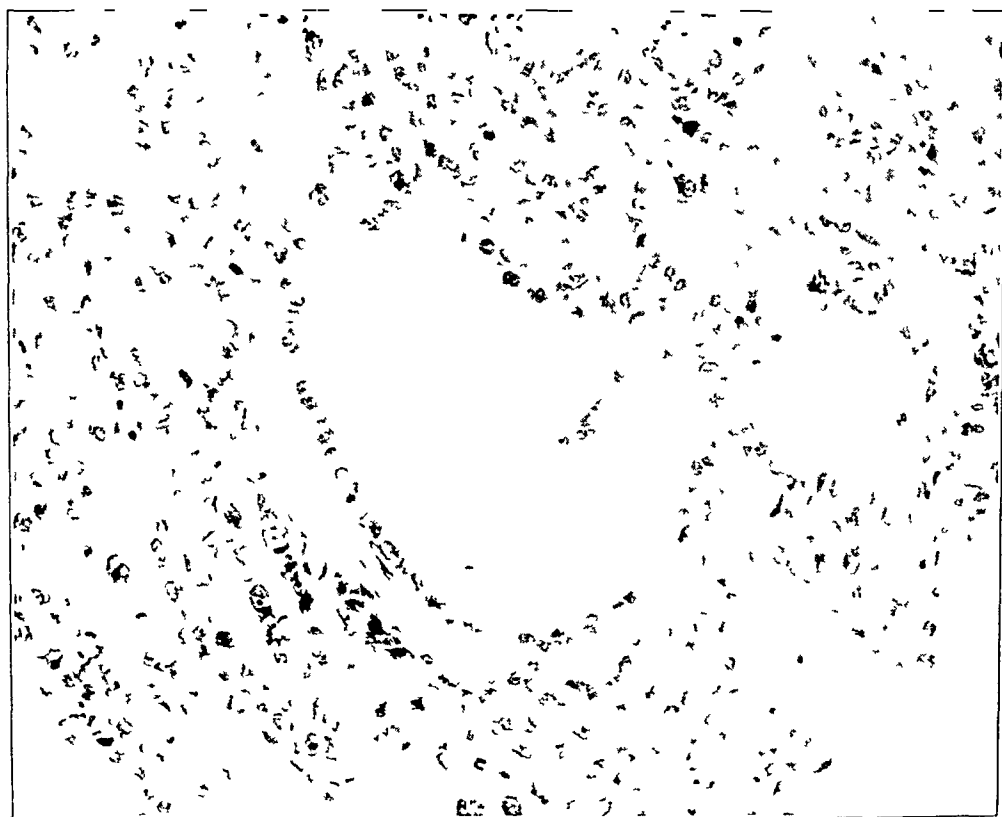


Fig. 11.—Dog 4. Terminal bronchus and alveoli with swollen and desquamated epithelium.  $\times 300$

left the room in which he was exposed to the vapor. The autopsy showed chiefly emphysema and edema of the lungs. Section of the lung had a violet red color and showed many bright red spots which were especially well aerated. A very abundant foamy, pale red fluid exuded from the cut surface. In the bronchi and trachea there was much thin foamy secretion with small amounts of thick mucus. The mucous membrane was a bluish red color. Microscopically the brain showed

4 Savels. *Deutsch med Wochenschr.* 1910 *xxvi*, 1754.

5 Loeschke. *Berlin path Anzt (Ziegler's)* 1910 *xlii* 457.

6 Czaplewski. *Vierteljahr f gerichtl Med* 1912 *xliii* 356.

7 Schubert. *Ztschr f Med-Berichte* 1911 *xxiv*, 557.

no lesions except small perivascular hemorrhages. The kidneys showed interstitial congestion with some necrosis in the ascending branch of Henle's loop. The lungs showed marked emphysema with intense congestion, the alveolar epithelium very largely desquamated and lay in masses in the alveoli. In the alveolar walls and also in the lumen there were numerous red cells and abundant leukocytes, and in some regions the walls of the alveoli were covered with a hyaline exudate. The mucous membrane of the bronchi was not altered microscopically. The liver showed nothing especially noteworthy.

CASE 2—Sch. Th. The patient was 41 years old and had always previously been well. While cleaning out the cellar he noticed no discomfort except irritation in the chest and occasional tendency to cough. After the accident he had a mild headache, some coughing without sputum and a feeling of weakness.

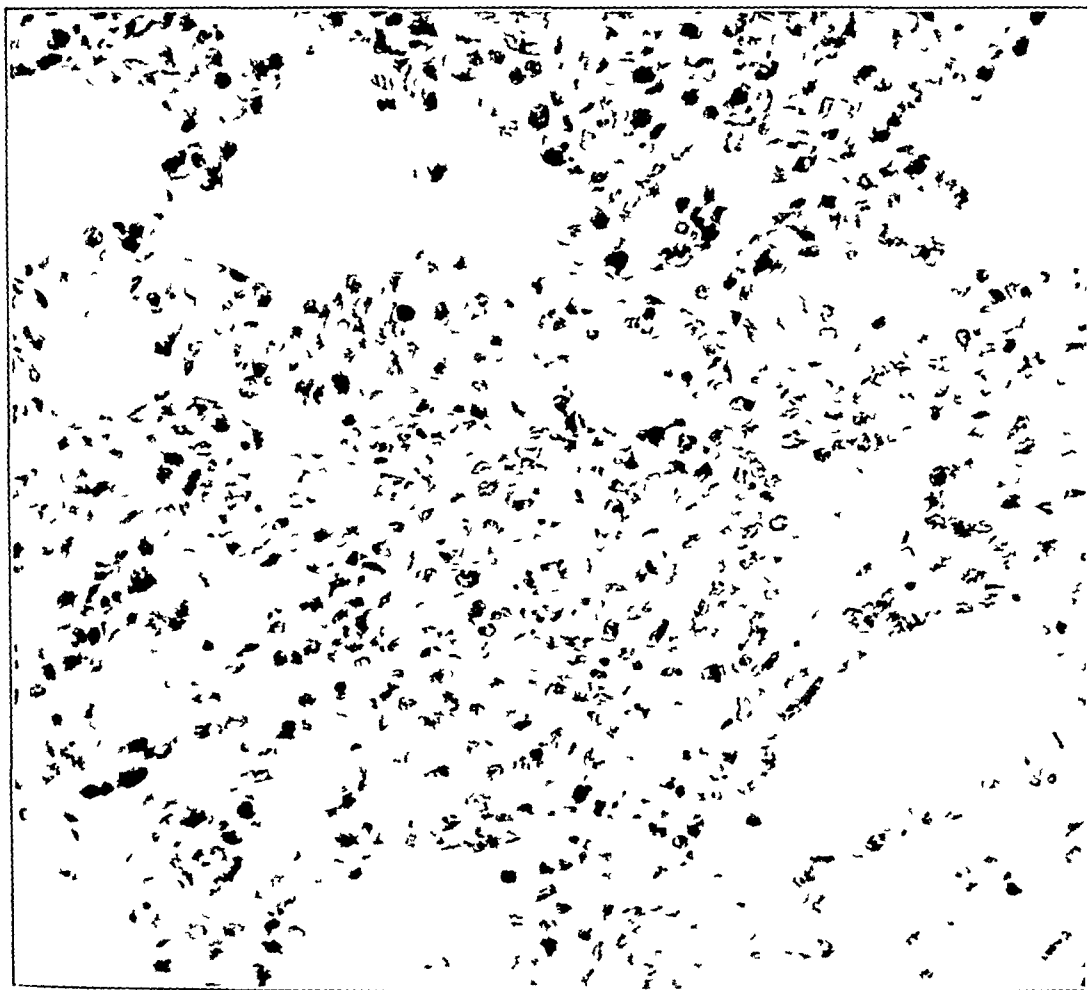


Fig 12—Dog 4 Desquamation of alveolar epithelium  $\times 300$

Three hours after the accident he had pain in the chest and a chill and went to bed but could not remain there on account of extreme dyspnea, a feeling of pressure on the chest, and violent coughing. He was taken to the hospital and on examination there was found to be extremely pale and cyanotic. Pupils were dilated and reacted slowly to light but otherwise there were no nervous symptoms. His mind was clear. Breathing was rapid and difficult with marked action of the auxiliary respiratory muscles. Over the lungs there were sonorous percussion notes with fine inspiratory crackles, no coughing, no sputum. The temperature was 101.1 F, the pulse was rapid 108, small and so. The heart sounds were pure. The patient had a venesection of 250 cc of blood.

which was strikingly dark and tar like, and coagulated rapidly, but spectroscopically showed only bands of oxyhemoglobin. There was a slight increase in the number of white cells. In spite of oxygen inhalations the patient became rapidly worse, he complained of a feeling of compression of the lungs, of intense thirst, and of frightful dyspnea. The face was covered with sweat, the eyes protruded and he could scarcely speak, the pulse became more rapid, rising to 140, and the temperature was 101.8 F. He died in coma forty-eight hours after the accident with signs of edema of the lungs, the final temperature being 102.9 F.

The urine passed during his stay in the hospital was small in amount, highly colored, faintly acid, free from albumin, and contained only 1 per cent of sugar. The ammonia was somewhat increased, acetone positive, acetoacetic tests negative.

Autopsy showed the lungs to be greatly distended, covering the pericardium, they were very heavy. The pleural surface was smooth. Sections showed a large

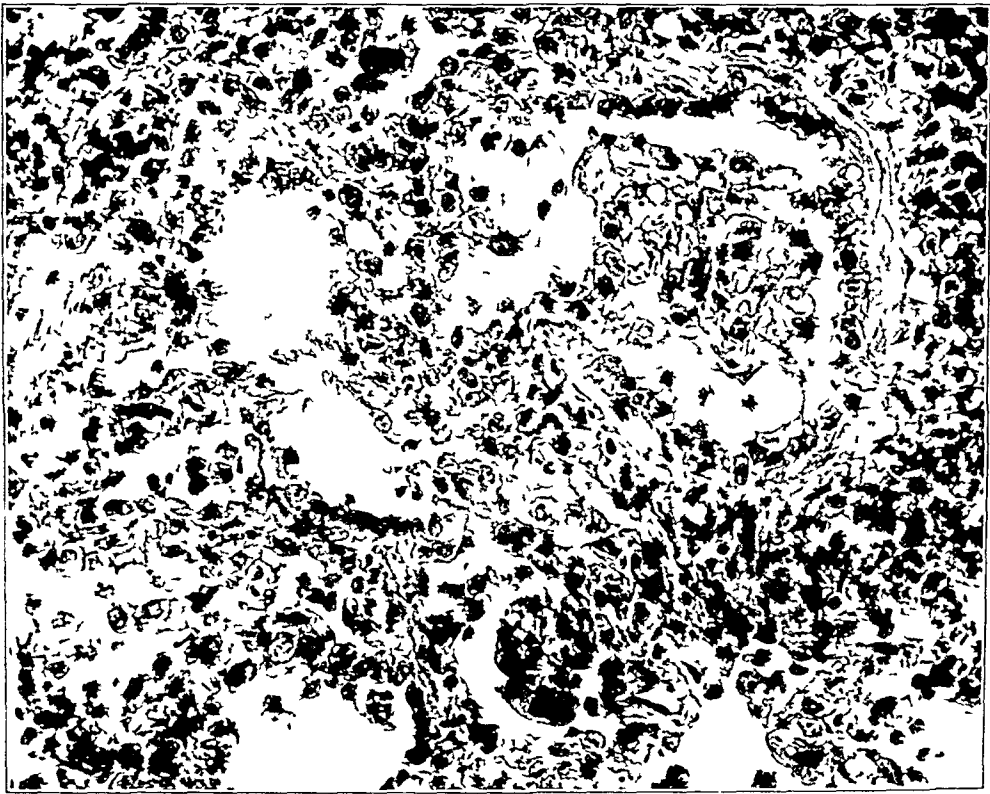


Fig. 13.—Dog 4. Intra-bronchial growth of epithelium.  $\times 300$

amount of edema and congestion with a general reddish color of the surface and numerous small granular areas scattered throughout, which were of a bright red color and emphysematous. The mucous membrane of the bronchi trachea and pharynx was of a bluish red color. The bronchial lymph nodes were large and swollen. The brain was intensely congested, otherwise there was no change. The kidneys also were intensely congested with no other change evident. The liver was pale and yellowish brown and blackened on the application of ammonium sulphid.

Microscopically there were no changes in the brain. In the lungs the alveoli showed great variations in the dimensions. There were areas of relatively narrow alveolar spaces filled with exudate partially fibrous partially hyaline and containing many red and white cells. Between such areas there were large, greatly

dilated spaces, chiefly without content apparently due to a traumatic emphysema as shown by the spaces where the torn walls were hyaline and thrombosed vessels lay near the site of rupture. The epithelial coating of the alveoli was desquamated that of the bronchi was present in areas though showing much degeneration, in other places it was entirely missing. All the vessels of the lung were greatly distended with blood. The spleen showed no special lesion except that there were many phagocytic cells containing blood pigment. The liver showed cloudy swelling with numerous areas of degeneration. At the periphery of these foci of necrosis there was already beginning repair with mitoses in the liver cells. In the kidneys the glomeruli tufts were very much distended filling the entire capsule. In some parts of the capsule there was a small amount of hyaline exudate with desquamation of the capsular epithelium. The cells of Henle's loop were completely necrotic and in the convoluted tubules there was much yellowish

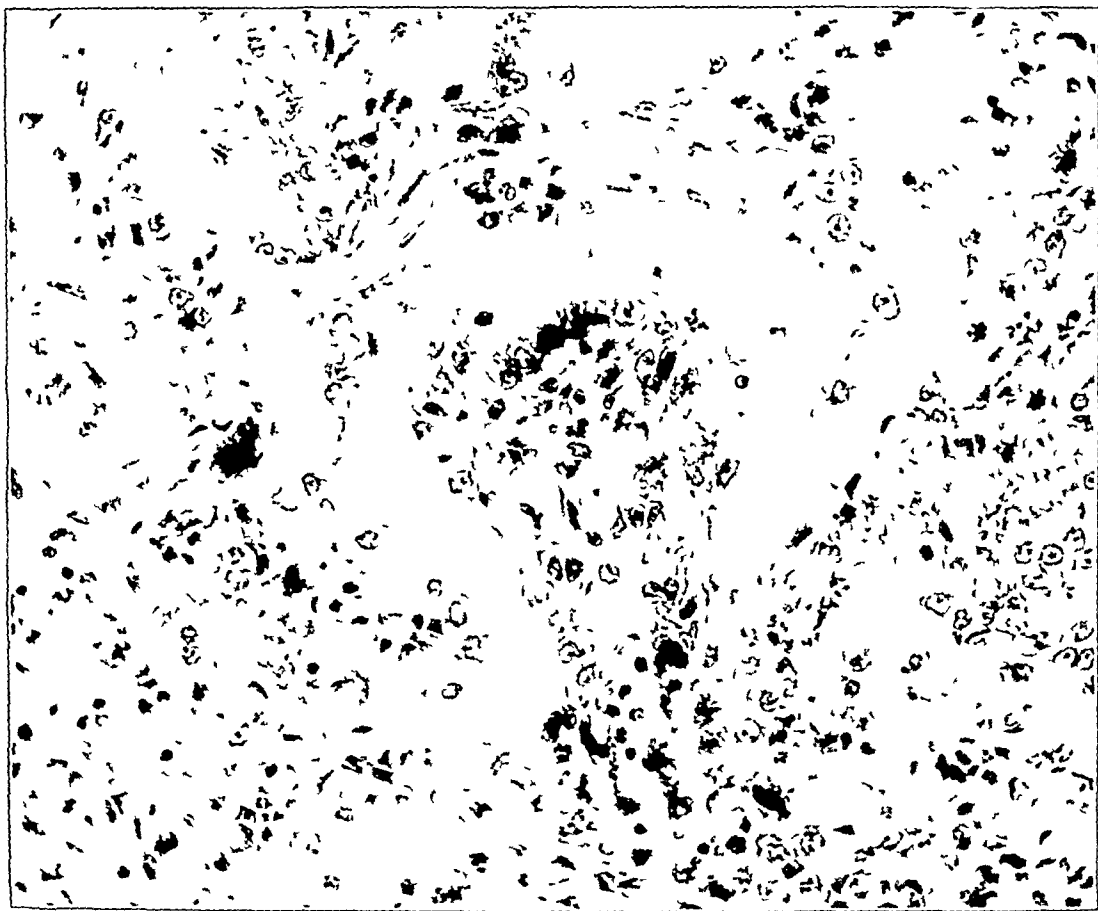


Fig. 14—Dog 1. Intra alveolar growth of epithelium  $\times 300$

granular pigment. Some of this pigment was contained in the tubular epithelium. Hyaline spherical granules were also found in the lumen of the tubules with an occasional hyaline cast.

CASE 3—W. W. Previous to the accident the patient had always been well. On entrance to the hospital he complained of moderate pains in the chest, coughing and slight dyspnea. On examination he was apparently a healthy man in good condition. The skin of the face was reddish, the mucous membranes were slightly exantheatic. Breathing was a little rapid, percussion sonorous. All over the lungs there were sibilant rales with a few moist rales over the lower right chest. The pulse was 108. There was some distention of the abdomen with diffuse tenderness. The stools were thin and yellowish. During the day the



patient expectorated some yellowish sputum and some faintly bronchial breathing appeared over the upper lobe of the right lung, and also in the left lower lobe there was moderate dulness with many respiratory rales. The temperature rose to 39 C. The blood obtained on venesection was dark and of a bluish color, but spectioscopically showed only oxyhemoglobin. There were no abnormalities in the urine. Two days after the accident the patient's mind was clear, he suffered from fever between 39 and 40 C with irregular remissions. There was bronchial breathing over the right upper lobe and left lower lobe, and edema over the rest of the lung. The sputum was brownish red, thin and foamy, and looked like pneumonic sputum, but no pneumococci could be found. Five days after the accident the patient had a moderate delirium. Venesection seemed to improve the general condition, but six days after the accident the heart action

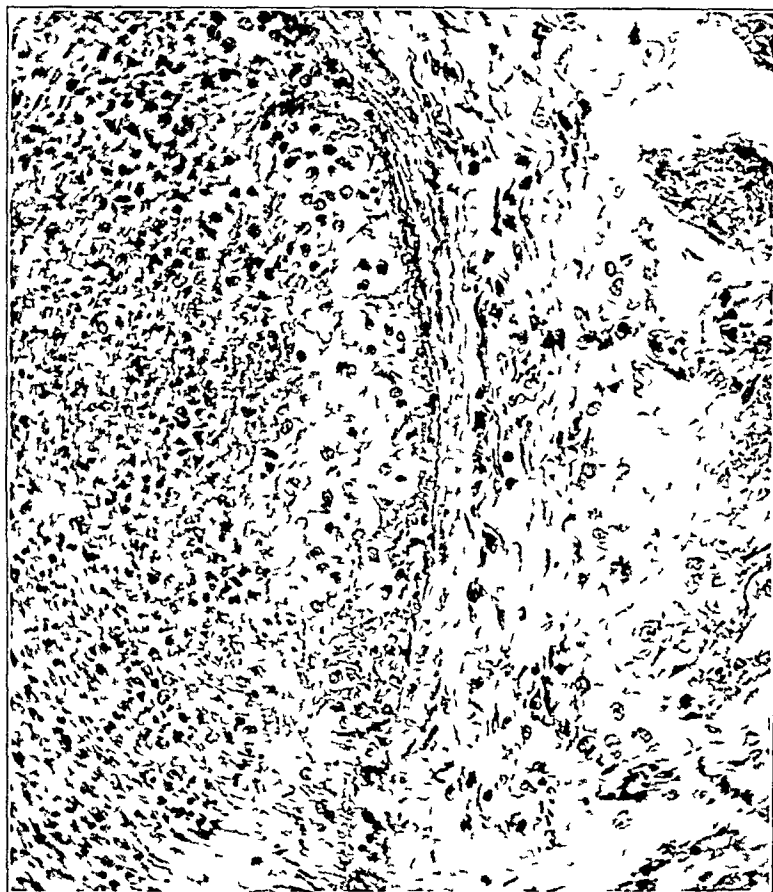


Fig 15—Dog 4 Thrombus in a vessel, blood clot to the left, lung tissue to the right  $\times 300$

became very feeble, the pulse was irregular, and the condition progressively became worse. The dyspnea increased, with restlessness and picking at the bed clothes. The patient died seven days after the accident with evidences of pneumonia and cardiac failure. At no time did the urine show any important changes.

The diagnosis at autopsy was croupous pneumonia in the upper lobe on the right side and the lower lobe on the left. Edema of the lungs, localized necrosis in the liver. The upper lobe of the right lung showed fresh adhesions. Both lungs were very large and heavy. On section the whole right upper lobe was granular in a state of red hepatization and absolutely free from air. There

were fibrinous plugs in the bronchi. The middle and lower lobes were edematous and contained some areas of pneumonia. The left upper lobe and the upper part of the lower lobe were extremely emphysematous. The lower part of the left lower lobe was largely granular, free from air, and in a state of red hepatization, with a few fibrinous plugs in the bronchi. The trachea and bronchi were filled with large amounts of foamy fluid. The liver was enlarged and intensely congested, and showed on cross section a grayish-red, cloudy appearance with some grayish areas scattered throughout. Both kidneys were very large, the capsules slightly adherent, the markings indistinct. The spleen showed intense congestion.

On microscopical examination of the lungs the alveoli in the pneumonic portion were partly of normal dimensions, partly very greatly dilated and filled with exudate which consisted chiefly of fibrin, but in places, of a smooth hyaline material. In this exudate there were found in varying numbers cells chiefly of polynuclear structure. In some regions the staining capacity of the alveolar wall was lost and in these areas the exudate seemed to have spread from one alveolus to another. The leukocytes were especially abundant here. Some of the blood vessels were thrombosed, but the blood-supply of the consolidated areas was slight. The alveolar epithelium was absent over considerable areas. In some places there were isolated epithelial cells with long projections extending over the alveolar wall, evidently a beginning regeneration. The projections came into contact with the nearest epithelial cells, and in this way large areas of alveolar substance had been covered with a few flat cells. In areas where the regeneration had gone further the cells were thicker and more cubical, though at the periphery of these areas they still retained the flattened form. The cell boundaries were often so obscured as to suggest syncytial structure. Finally, some alveoli were entirely covered with cubical epithelium, occasionally much higher than the normal. No mitoses were observed. The epithelium of the smaller bronchi was still preserved. In the portions of the lung not involved in the pneumonia the alveoli were partly free from exudate and partly contained larger or smaller amounts of fibrin, leukocytes and red cells. The fibrin in places had undergone hyaline degeneration. The epithelial regeneration in these areas had progressed further than in the hepatized portions, so that most of the alveoli were covered with a thin, flat epithelial layer. No bacteria could be found.

Section of the liver showed areas of necrosis in the center of practically all of the acini. The central vein was frequently thrombosed. Polynuclear leukocytes were scattered through the necrotic tissue. The liver cells at the periphery of the acini were large, their nuclei rich in chromatin, and showed mitoses. Pigmentation of the liver cells was slight in amount.

The glomeruli of the kidney were large, the capsules were thin, with moderate desquamation of the capsular epithelium. In the capsules were found finely granular masses of albumin, in places compressing the glomerulus. The epithelium of the convoluted tubules was swollen, and many cells showed imperfect staining qualities. The lumen of the tubules contained granular masses of albumin. In Henle's loop there was extensive necrosis of cells, many of which had fallen off in the lumen. The collecting tubules showed numerous small homogeneous casts composed apparently of masses of tubular epithelium. They stained dark with hematoxylin and black with silver, in other words, they probably contained some phosphate of lime, a condition found chiefly in cases of poisoning with mercuric chloride.

CASE 1.—A. S. This patient was not engaged in cleaning up the acid, which had been completed but as night watchman had to pass through the cellar every hour. During the day following his night work he complained of pain in the chest and abdomen. When examined he was found to have symptoms of a severe bronchitis with very rapid and irregular heart. He complained also of dizziness and faintness and vomited a good deal. Twelve days after the accident he was seized suddenly with a cerebral hemorrhage and died three days later. Autopsy showed extensive arteriosclerosis with an area of red softening

about 2 cm in diameter in the left posterior portion of the internal capsule. The hemorrhage was encapsulated but had broken through into the ventricle, which was filled with fluid blood. In this case the influence of the nitric oxide fumes was probably entirely secondary, as the lungs showed no lesions, but the coughing and vomiting may have induced the cerebral hemorrhage.

This completes the Cologne series. The following reports, while in the main less complete, are of sufficient importance to warrant their inclusion.

CASE 5—This is an exceedingly interesting case reported under the title "bronchiolitis fibrosa obliterans."<sup>8</sup> The patient survived the inhalation of the nitrogen tetroxide for nineteen days, so that the description shows well the nature of the lesions and the repair which takes place in a long continued case. From the microscopical findings given it is evident that the regeneration of the alveolar epithelium was nearly complete, though the cut shows some alveoli still filled with large cells, but in any case the desquamative lesions of the lungs were less striking than the organization and closure of the bronchi and small vessels with new-formed tissue.

The patient was a laborer, 25 years old, who was previously healthy, he inhaled the fumes from a vessel containing nitric and sulphuric acids with a piece of brass casting. (Such a combination gives nitrogen tetroxide vapors.) Immediately afterward he had a severe attack of coughing with a feeling of oppression on the chest and a good deal of pain in this region. During the course of the night following he was seized with intense dyspnea and entered the hospital. On admission it was noted that he was intensely cyanotic, temperature, 102, pulse, 112, respirations, 72, blood-pressure, 105 mm. There was slight dulness over both lungs posteriorly and coarse and fine crepitant râles all over. The patient complained of a feeling of burning behind the sternum. The sputum was small in quantity, reddish-brown and mucoid. The following day the temperature was normal and the cyanosis and dyspnea diminished. Respiration went down to 60, and the pulse to 108. The râles in the anterior portion of the chest diminished. Two days after the accident the patient coughed up rust-colored balls of sputum, showing very few diplococci. From the third to the seventh day after the accident the temperature rose slightly, and there was subcutaneous emphysema of the anterior thorax between the second and fifth ribs. Eight days after the accident the subcutaneous emphysema disappeared and the patient was in fairly good condition without symptoms, except a few râles in the chest, until four days later when the cyanosis and dyspnea returned. The respirations rose to 60 and the pulse to 120. The condition was not so serious as at the first attack. The râles returned with a change in the percussion note. The sputum was reddish-brown and mucoid. The patient died nineteen days after the accident.

At autopsy, the heart showed slight hypertrophy of the right side. The lungs were very much dilated, so that their borders touched each other at the level of the second and fourth ribs. A few fibrinous adhesions at the left apex and left lower lobe. On the surface of the lung there were a number of somewhat depressed bluish spots of irregular outline which contained less air than the rest of the tissue. On section, these were edematous. Scattered throughout the lung also were small areas of hepatization. In addition there were numerous small nodules of a transparent gray color looking a good deal like tubercles. The small vessels contained thrombi. The right lung also was voluminous and distended with air. In the middle lobe there was an area of hepatization about the size of a cherry. On the surface were numerous bluish red spots, on the pleural surface of which were small fibrinous coagula. The cut surface showed

many irregular dark-red areas, and besides these, small grayish white nodules attached to the smaller bronchi. There was an emphysema of the lung with numerous areas 2 to 3 mm in diameter. The smaller arteries showed thrombi adherent to the walls. The other organs showed nothing but congestion.

Microscopical examination of the lung showed a large number of thrombosed small arteries and the hemorrhagic and edematous areas which Fraenkel was inclined to interpret as small infarcts. In the fine terminal bronchi there was a marked epithelial desquamation, the cells often filling the entire lumen. The larger bronchi also showed considerable loss of epithelium. In the finer branches of the terminal bronchi there was a growth of connective tissue reducing the lumen in many cases to a small slit, covered in part with high cylindrical epithelium of the bronchial type. The remainder of the lung showed either emphysema, edema or collapse. In the denser portions the alveolar walls were thickened with connective tissue, especially near the bronchioles. Some of the vascular thrombi had undergone complete organization with the formation of connective tissue. There was no report of any bacteriological examination of the lung tissues.

In a later paper Fraenkel<sup>9</sup> reports three more cases of so called bronchiolitis obliterans fibrosa acuta, one in a plasterer who inhaled a large amount of lime and other dust, and the second in a man working in a drug store. The history of this latter case was very imperfect and Fraenkel says that it was not possible to exclude the inhalation of some irritating substance as the cause of the disease. In the third case reported no history was obtainable, and the diagnosis was made solely on the clinical symptoms of intense dyspnea, cyanosis and emphysema. Death occurred on the fourteenth day. Microscopical examination of the tissues showed chiefly obliteration of the bronchi.

The report is not very clear, but apparently all these patients lived for at least two weeks. The writer also observed another case with similar symptoms due to the inhalation of large quantities of dust from chlorid of lime. He says, however, that the disease is not always due to the inhalation of irritating gases or powders, and that measles and whooping-cough occasionally produce in children a very similar anatomical picture. In ordinary lobar pneumonia such a closure of the bronchi by the ingrowth of connective tissue does not occur or is very limited in extent, even in cases in which resolution is prolonged over weeks.

CASE 6—The patient,<sup>10</sup> 23 years old, a tinner by trade, inhaled the fumes from a mixture of hydrochloric and nitric acids. He had a slight oppression in the chest but continued at work for nine days though not feeling well. On the tenth day he had a good deal of dyspnea and entered the hospital. When examined he showed very marked cyanosis, especially of the face. Thoracic movements were limited during respiration, which was rapid and shallow. The pulse was 140, very soft and irregular. Temperature was 102.2 F. There was dulness over the chest. The patient appeared moribund. The sputum was abundant, yellowish and lumpy. There were physical signs of emphysema with many moist rales over the lungs. The next day respiration went to 50, the temperature was about 100.4 F, the cyanosis and dyspnea increased, and the patient died twenty six days after the exposure to the fumes. At autopsy the lungs did not collapse on opening the thorax. There were small hemorrhages in the pleural surfaces of the lower lobes. On section the lungs were densely sprinkled with small grayish nodules 1 to 2 mm in diameter, which surrounded the smaller

<sup>9</sup> Fraenkel. Berl klin Wchnschr, 1909 xlv 6

<sup>10</sup> Edens. Deutsch Arch f klin Med, 1906 lxxx 598

bronchi. The mucous membrane of the larynx, trachea and smaller bronchi was intensely irritated, and in many places had disappeared. No other lesions were found in the body.

Microscopic examination showed marked inflammatory lesions of the trachea and bronchi with congestion and edema. In the lung there were numerous small chronic pneumonic areas with the formation of granulation tissue. The alveoli at the periphery of the pneumonic areas contained a cellular exudate chiefly composed of desquamated alveolar epithelium, the cells being of large size and often loaded with pigment. Some of the alveoli also contain fibrin. There was marked inflammation of the septa of the alveoli with edema, fibrinous exudate and leukocytes, the vessels were greatly distended. Thrombi were not noticed, and bacteria were not found in the lung sections.

This case is particularly interesting because of the long continuance of the disease, showing the latter stages of the process, death usually occurring much earlier in the course of the intoxication.

CASE 7—Paul<sup>11</sup> reports the case of a laborer, 32 years of age, who was ordered to clean the deposit out of a lead chamber. This deposit consisted chiefly of lead sulphate mixed with some sulphuric acid, the mixture giving off vapors of some of the nitric oxides. For this reason it was necessary that the workers leave the chamber every few minutes as the stirring up of the mud set free the fumes. The chamber had been cleaned some two hundred times under exactly the same conditions as on the occasion of the accident. There were two other workers also in the chamber who were not in the least affected. The patient entered the chamber three times, remaining for periods of ten to twelve minutes. About 6 o'clock he went home without complaining in the slightest. Some hours afterward, however, he was seized with dyspnea and very severe coughing. He attempted to go to work the next morning, but collapsed on reaching the factory. The patient was examined by a physician after his collapse at the factory and was found to be intensely dyspneic with paroxysms of coughing. The sputum was brownish-red in color, having previously been bright yellow. The lungs showed some dulness over the lower lobes, but no bronchial breathing, only fine râles all over. The pulse was 110, very soft and small. Temperature was subnormal. About thirty hours after the exposure he had a severe seizure with extreme cyanosis, great restlessness and occasional delirium. He went into coma and died about forty-six hours after exposure to the gases with the symptoms of pulmonary edema.

Autopsy showed intense congestion of the membranes and substance of the brain with numerous punctate hemorrhages in the substance. The mucous membrane of the pharynx, trachea and larynx was very dark red and covered with sticky mucus. The heart's blood was very dark, the organ was dilated and the muscle was soft. The pleura of the right lung showed a number of small ecchymotic areas about 1 cm in diameter. On section a large amount of reddish, foamy fluid escaped from the lung which was extremely edematous, with the peripheral portions showing a considerable amount of emphysema. Section of the left lung showed the same but the pleura was adherent all over the thorax with old adhesions. The stomach showed a small hemorrhagic erosion at the greater curvature. There was no lesion except intense congestion of the viscera. No microscopic examination was reported.

CASE 8—Schmieden<sup>12</sup> reported the case of a 24-year-old laborer who was exposed to nitrogen tetroxide fumes for one hour following the breaking of a carboy of nitric acid and attempts to stop the action of the acid by the use of sawdust. He noticed only slight dyspnea after finishing the work and on his return home

11 Paul Wien klin Wehnschr, 1895, viii, 665

12 Schmieden Centralbl f klin Med, 1892, xiii, 209

some cyanosis. During the night the patient was unable to sleep on account of increasing dyspnea and very severe cough. On admission to the hospital he was found to be intensely cyanotic, respirations, 78, breathing chiefly abdominal with marked movements of the alae nasi and the sternocleidomastoid and scalenus muscles. Percussion note was tympanic. Fine rales were heard all over the chest. The sputum was abundant, thin, rusty-brown in color like pneumonic sputum after edema of the lungs supervenes. The pulse was 112 and soft. Blood taken from the ear was brownish black in color and on dilution in water became bright red, spectroscopically there was nothing abnormal. The patient died in coma thirty hours after the inhalation of the acid fumes with symptoms of edema of the lungs.

At autopsy the lungs were extraordinarily congested and infiltrated throughout with bloody edematous fluid. The mucous membrane of the bronchi was congested. The vessels of the lungs were distended with dark red and black thrombi. There was intense congestion of the pial veins and the arteries at the base of the brain. There was a yellowish slough on the mucous membrane of the stomach near the cardia. No microscopical examination was made.

CASE 9—Kockel<sup>13</sup> reported the case of an apparently healthy male, 65 years old, who had worked for about one hour in a room in which a large quantity of nitric acid had been spilled. Except for a little coughing and dryness in the throat there were no symptoms until six hours after exposure, when he was seized with very severe dyspnea, coughing, and a feeling of great anxiety. The symptoms increased rapidly with intense cyanosis, and the patient died two hours later. At the autopsy there was congestion of the meninges, in the posterior portion of the external rim of the right lenticular nucleus there was an area of softening the size of a hazel nut, apparently an old lesion. The heart muscle was soft, the cavities were much dilated and filled with dark fluid blood. The left lung was very voluminous, the tissues were soft and tore easily, and on cut section were very dark grayish-red. There was a good deal of edema and very little air in the alveoli. The right lung also was very voluminous, the upper lobe dark grayish-red and very much congested with only a moderate amount of fluid in the alveoli. The mucous membrane of the larynx, trachea and bronchi was bright red and much swollen. No microscopical examination was reported.

In addition to these reports of fatal cases with complete autopsies, there are a considerable number of reports of fatal cases with partial autopsies, and also of cases of mild types of poisoning, some of which are of sufficient interest to reproduce here.

Orfila<sup>14</sup> collected two cases. In the first case, observed by Desgranges<sup>15</sup> the fumes were evolved by the breaking of a flask of nitric acid, exposure lasting for about five minutes. The patient then went into the open air and recovered from the sensation of choking. He was very thirsty about four hours later, and twelve hours after exposure was seized with coughing and prostration, and seventeen hours after the accident had an attack of intense dyspnea with cyanosis, pain in the abdomen, convulsive movements, and delirium, and died about twenty-seven hours after the inhalation of the gas. There was no autopsy.

In the second case,<sup>16</sup> a healthy man of 22 years inhaled a large amount of fumes set free on the breaking of a flask of nitric acid. Some hours afterward he took a walk in order to relieve a sensation of oppression in the chest. About nine hours after the accident intense dyspnea supervened. Forty-eight hours

13 Kockel *Vierteljahr f gerichtl Med*, 1898, xv 1

14 Orfila *Toxicologie*, Trans by Kuhn, Leipzig 1839 i, 124

15 Desgranges *Jour de mcd. continué* 1804 viii 487

16 Cherrier *Bull Soc mcd Emul* 1823

after the gas was inhaled the patient died with typical symptoms. At autopsy the right lung was found to fill the entire half of the thorax, it was solid and edematous, most of the fluid appearing to be dark fluid blood. In the left lung there were large amounts of bloody fluid but some of the parenchyma was still well aerated. The mucous membrane of the trachea and bronchi was of a blood-ied color. There were superficial ulcerations in the cardia and pylorus. The contents of the stomach were sour. The other organs showed no changes.

In a third case,<sup>17</sup> a powerful man, 34 years old, was cleaning copper with nitric acid. After two days, during which time he had inhaled a considerable amount of the fumes of the acid, he was seized with headache, cough and oppression in the chest. Twenty-four hours later on examination he was found to have intense dyspnea, protruding eyes, purple lips, and frequent cough, with sticky, yellow sputum. There were coarse râles over the chest. He died twenty-four hours after the onset of the symptoms. At autopsy the lungs were very voluminous, crepitant and of normal color. The mucous membrane of the trachea and bronchi was vivid red and much swollen. The bronchi contained much yellow fluid and a similar fluid could be expressed from the lung tissue on section.

Manouvriez<sup>18</sup> reported several cases, the exposure occurring when a warehouse containing sodium nitrate and other substances caught fire. One of the workmen made several attempts to remove the sacks and was exposed for a few minutes each time to the vapors of nitrogen tetroxide. After the third attempt he collapsed and was taken to his home. He complained of thirst and intense dyspnea with intense pain in the chest, and died about four hours after the exposure. His assistant died with the same symptoms about eight hours after the exposure. Another exposed person suffered from violent vomiting and diarrhea, but was ill for only two days.

Autopsies on the first two cases showed that the blood was black and acid to litmus paper, the latter seeming a rather remarkable condition in the light of our present knowledge of the great acid-neutralizing capacity of the blood and the fact that a change in reaction was not noted in any of the animal experiments which follow. There was intense congestion of the bronchi and lungs which were distended with blood and contained several areas of hemorrhage. Hyperemia of the mucous membrane of the stomach was noted, with congestion of the other organs.

Kunne<sup>19</sup> reported briefly eleven cases of intoxication due to the inhalation for only two or three minutes of fumes arising during a fire in a building in which a large number of carboys of nitric acid were stored. In some of the cases no symptoms appeared until six or eight hours afterward, the patients having stood about watching the fire, smoking their pipes, etc., and finally going home to bed and to sleep. They were awakened by intense dyspnea. Some of the patients vomited, and showed great cyanosis, nervous symptoms, and rapid and fatal heart action. There were two fatal cases, but these were not observed by Kunne. Seven of the patients ran a mild course and were discharged nine days after the exposure as cured. Four others were much more seriously affected and were not able to return to work for two weeks after the exposure. The only exceptional point was that three of the patients showed albumin in the urine. All the others had the usual symptoms previously described.

Pearse<sup>20</sup> reported the case of a man, 35 years of age, who inhaled the fumes of nitrogen tetroxide on the breaking of a carboy of nitric acid. Six hours after the inhalation the patient had pains in the chest and difficulty in swallowing and talking. Eight and a half hours after inhaling the fumes he had an attack of

17 Suequet. Details are given by Chevallier and de Loury, *Ann. d'hyg.*, 1847, *xxviii*, 323.

18 Manouvriez. *Bull. de l'acad. de m'ed.*, Paris, 1897, *xxviii*, series 3, p. 306.

19 Kunne. *Deutsch. med. Wchnschr.*, 1897, *xxiii*, 414.

20 Pearse. *Albany Med. Ann.*, 1899, *xx*, 28.

severe dyspnea, respirations, 40, high pitched respiratory murmurs over bronchi and right lung. The left lung was not involved. Bloody mucus was expectorated. Twenty-four hours after the accident signs of consolidation developed in the right lung with edema and cyanosis of the lips. The patient became delirious and died twenty nine hours after inhaling the fumes, of edema of the lungs.

Wood and Stephen<sup>21</sup> reported the case of a chemist who broke a bottle containing about three liters of nitric acid, and spent about half an hour in cleaning up the fluid by means of sawdust and cloth, he was not inconvenienced by the fumes. Eight and a half hours after the accident he began to suffer from intense dyspnea and expectorated large quantities of straw-colored fluid, nearly a liter in amount. Respirations, 62, marked cyanosis and very violent cough on the first day, cough less on the second day, none after the third day. Recovery was slow, the patient remaining in bed for ten days.

Harrington<sup>22</sup> reported nine cases of poisoning by nitrogen tetroxid fumes following the breaking of a carboy containing nitric acid. None of the patients felt any bad effects until five to eight hours after the exposure, when they developed dyspnea, rapid respiration, cough, and in some cases delirium. There were no fatalities.

Lange<sup>23</sup> reported two cases of an organizing bronchitis which do not correspond either in the clinical history or in the general autopsy findings with the type of disease due to inhalation of irritating gases and are here quoted merely because they are frequently referred to in the literature of the subject. In the first case there was a history of cough for eight days, chills and headache, the patient entering a hospital and dying on the ninth day of the disease with a pneumonia, showing subpleural hemorrhages and numerous gray miliary nodules throughout the lung tissue, which proved to be fine terminal bronchi. Each small nodule was surrounded by about 1 mm. of dark colored lung tissue. The alveoli lying between these nodules showed no exudation. In the second case, the patient, 32 years old, had been sick for six months with cough and dyspnea. For four weeks before death he had great discomfort so that he was not able to work. Autopsy showed voluminous lungs, hemorrhagic spots in the pleura, and on the cut surface large numbers of small nodules which looked like miliary tubercles. These grayish nodules were surrounded by a narrow ring of reddish tissue. The lung between these areas was quite normal. The vessels showed no thrombi.

Pott<sup>24</sup> reported an instance in which nitrogen tetroxid fumes were formed by the action of acid phosphate on sodium nitrate, the mixture being a preparation used as a fertilizer. About thirty persons were exposed to the vapors, of whom two died, one in twelve hours and one in forty hours. There was no autopsy in either case. The symptoms were typical as described above. Eight persons were confined to bed for a number of days with very severe dyspnea and cough, the sputum being thick and yellow and containing blood and alveolar epithelium. In the most serious case the patient was confined to bed for eight days, but recovery was complete.

Hall and Cooper<sup>25</sup> reported a case in which a carboy of nitric acid was accidentally broken and the acid spread over the floor, attacking some zinc plates and sawdust and starting a fire. Twenty people were seriously affected, four of whom died, two on the second day and two several weeks later. Dyspnea was present in 100 per cent of the cases, cough in 93 per cent, vomiting in 53 per cent. Cough with bloody expectoration persisted in 27 per cent. The patients who recovered were found to be more susceptible to cold than before. Two cases were autopsied. The records are very incomplete, it is stated that in one the lungs were large and voluminous and the bronchi filled with bloody

21 Wood and Stephen. Australasian Med Gaz, 1909, xxviii, 25.

22 Harrington. Wisconsin Med Jour, 1903, 1, 177.

23 Lange. Deutsch Arch f klin Med, 1901 lxx, 342.

24 Pott. Deutsch med Wehnschr, 1884, x, 451.

25 Hall and Cooper. Jour Am Med Assn, 1905 xlv 396.



fluid There was much edema of the lung tissue and a thickening of the bronchial mucosa The second case in which death occurred one month after exposure showed bronchopneumonia with consolidation of the lung, and microscopically the alveoli were filled with cells and beginning fibrosis

Bauer<sup>25</sup> reported a case of an anilin factory worker who inhaled nitrogen tetroxid After a short time he had dyspnea and cough, and he died in two days with pulmonary edema An autopsy showed acute bronchitis, lobular pneumonia and edema, with thrombi in the pulmonary vessels

#### ANIMAL EXPERIMENTS

In order to study further the lesions seen in the reported case, a series of experiments were carried out on dogs

Among those who had made previous studies of acid poisoning on animals may be mentioned Lesser,<sup>27</sup> who exposed rabbits and dogs to the vapors given off on warming nitric acid He showed that only occasionally bronchitis, bronchopneumonia, or edema of the lungs supervened Even after exposing dogs for weeks to acid vapors he was not able to find any microscopical changes in the lungs The reason for this is that the acid volatilizes unchanged and condenses in the nasal passages, and while it may corrode the tissues there does not penetrate further Practically no nitrogen tetroxid is given off from ordinary nitric acid on warming

Kockel, Bauer,<sup>26</sup> Gréhant and Quinquaud,<sup>28</sup> and Eulenberg<sup>29</sup> carried out animal experiments with nitrogen tetroxid Those of Gréhant and Quinquaud and Eulenberg are not important here because the animals either died within a few minutes or recovered from the inhalation, and no microscopical examinations were made

Kockel's animal experiments gave the following results <sup>13</sup> The blood of the animals dying in an atmosphere of nitrogen tetroxid fumes had a chocolate-brown color, but when the animals had a chance to breathe fresh air for a few minutes after inhalation of the gas, the blood was merely dark in color and not otherwise abnormal The lungs were usually markedly emphysematous, the color was almost always bright red, and on section there were usually reddish areas and much edema Extensive hepatization was noted only in the animals killed four or five days after the exposure to the fumes The mucous membrane of the respiratory passages was congested and edematous The spleen and kidneys showed no gross lesions The liver was occasionally intensely congested In some animals swelling, edema and ulceration of the mucous membrane of the stomach and intestine was observed Microscopically, the chief lesion in the lungs was intense hyperemia with

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<sup>26</sup> Bauer Original report not accessible Few details given Abstract in Virchow-Hirsch Jahresb 1895 p 460

<sup>27</sup> Lesser Ztschr f physiol Chem 1877, 1, 165

<sup>28</sup> Gréhant and Quinquaud Compt rend Soc de biol, 1884, viii, t 1, 469

<sup>29</sup> Eulenberg Vrtljschr f gerichtl Med, 1876, xxv 209

hyaline thrombi in the capillaries, a condition also observed by Bauer. Thrombi also were found in the larger vessels leading to the lungs in some cases. An extensive edema of the lung tissue involving the perivascular and peribronchial connective tissue and also the alveolar walls was quite common. Over areas of moderate extent in the lungs the alveoli contained serous or fibrinous exudate. In the animals which survived for a number of days there was almost always a bronchopneumonia, the alveoli being filled with red and white cells and desquamated epithelium. Four or five days after the inhalation a considerable pneumonic infiltration was usually present, the alveoli being filled with desquamated epithelium, which not infrequently fused to syncytial-like masses. The parts of the lungs free from edema and exudate were emphysematous. Plugs of epithelium and leukocytes cemented with mucus often filled the smaller bronchi. Multiple focal necroses were occasionally present in the liver.

Spectroscopical examination of the blood showed that the chocolate-brown color observed in the animals dying in an atmosphere of nitrogen tetroxid fumes was due to the formation of hematin. This substance was also observed by Kobert in the urine of a patient, but is not as a rule demonstrable in those patients who have survived exposure to the gases. Probably only very small amounts of this substance are formed in the blood. No morphological changes in the circulating blood were noted.

The necroses occasionally observed in the mucous membrane of the stomach and intestine were undoubtedly due to the fact that some of the fumes had dissolved in the saliva and been swallowed, causing erosions. The results of the animal experiments, therefore, correspond quite closely with the lesions found in human beings.

My own experiments confirm and extend Kockel's results. A few characteristic protocols are appended. Dogs were selected for the experiments because of the ease with which pneumonia is induced in these animals and because the lungs are voluminous enough to permit of considerable topographical variation in the pneumonic areas.

Dog 1—Large, powerful animal weighing about 15 kilos, was anesthetized with ether and allowed to fill his lungs four times with fumes of nitrogen tetroxid mixed with about an equal volume of air. The animal revived from the ether and seemed pretty well for some hours but on the following morning was suffering from severe dyspnea both inspiratory and expiratory. He remained quietly in his cage and refused to eat. He coughed a good deal, and forty-eight hours later was killed. The lungs showed an acute bronchitis with edema, desquamation of the bronchial epithelium, and a small amount of lobular pneumonia, the alveoli containing large cells, many of them pigmented, and a good deal of fibrin and a few leukocytes. The remainder of the lung was deeply congested and showed a good deal of edema with a marked emphysema especially in the anterior portions. The other organs showed no lesions. Cultures from the lungs were sterile. The condition corresponds to that noted in persons dying soon after inhaling the gas.

Dog 3—Terrier, weighing about 10 kilos, was lightly chloroformed and allowed to fill his lungs about twelve times with a mixture of equal volumes of air and nitrogen tetroxid. The animal died about ten minutes later and on removal the lungs were found to be almost solid with edematous bloody fluid. Microscopically the alveoli were filled with a serous edema containing many red cells. No lesions were present in the other organs. A similar condition has been noted in some of the rapidly fatal human cases.

Dog 4—Terrier, weighing about 9 kilos, was lightly chloroformed and allowed to fill his lungs three times with a dilute mixture of air and nitrogen tetroxid. It soon recovered but refused to eat, had a good deal of difficulty in breathing, with coarse râles over the chest, and coughed a good deal, raising yellowish frothy mucoid sputum. The animal was killed after five days. The lungs showed extreme emphysema with a scattered lobular pneumonia (Fig 2) most marked in dependent portions. The bronchi were congested and filled with mucus. There were no other macroscopic lesions. Microscopically the lungs showed extensive lesions, the other organs were normal except for a few focal necroses in the liver. The bronchial mucosa was extremely edematous and congested, but the epithelium was still intact (Fig 10), the cilia even being present in a few areas. The epithelium of the terminal bronchi was swollen and desquamated (Fig 11), as was that of the alveoli (Fig 12). The alveolar walls were thickened and edematous, and the capillaries congested. Emphysematous areas alternated with patches of pneumonia (Fig 2). There were plugs of epithelium in the terminal bronchi (Fig 13), some of them composed wholly of cells, others of cells covering a growth of fibrous tissue. This is the lesion described by Fraenkel as "bronchiolitis fibrosa obliterans." Similar plugs filled some of the alveoli (Fig 14), others contained solid masses of desquamated cells, others were filled with blood, fibrin and coagulated serum, still others were lined with unregenerating epithelium. Mitotic figures were rare, though present. A number of the smaller vessels showed thrombi in various stages of organization (Fig 15). The lesions in the lungs were very irregularly distributed and corresponded very closely in all details with those of the case of D, here reported, except perhaps in the extent of the emphysema, this lesion being less marked in the dog than in the human material, while the bronchiectasis was more extensive in the animal.

Dog 5—Irish terrier, weighing 7 kilos, was etherized and given ten breaths of very dilute nitrogen tetroxid. Nineteen days later the dog still had a cough but otherwise seemed well. It was then given four deep breaths of dilute nitrogen tetroxid, and eighteen days later three inhalations of the same. Six weeks later it was killed. The lungs seemed normal in the gross, and microscopically it could not be determined that there were any changes, possibly the lungs were slightly more emphysematous than those of a normal dog, but repair was extraordinarily complete.

Dog 6—Fox terrier, weighing about 9.5 kilos, was given, under ether anesthesia, six breaths of dilute nitrogen tetroxid and air mixture. The following day the dog was very quiet, did not seem to suffer very much pain, but coughed a good deal and showed intense dyspnea. The second day after he coughed up thin, foamy sputum, did not eat, and vomited small quantities of mucus, for six days he coughed continuously and was then killed. On opening the thorax the lungs were found to be covered with a thin layer of fresh fibrin which was especially abundant over patchy areas of deep congestion. These congested areas were scattered irregularly throughout, and were especially abundant near the thin edges of the lobes, they were quite firm to pressure. The remainder of the lung was well aerated. The bronchi were filled with thick mucus, the mucous membrane was congested. The bronchial lymph-nodes were not enlarged. The kidneys and other organs appeared normal. The brain showed no hemorrhages nor softening. Microscopically the lungs showed irregular areas of lobular pneumonia with fibrin, a few leukocytes, and many desquamated alveolar epithelial cells. There was considerable fusion of the alveoli to form large open spaces.

The alveolar walls were much thickened and congested. There was beginning repair of the epithelium in some of the alveoli. The kidneys and liver showed no microscopical changes. Cultures from the lung were sterile.

Dog 7—Short-haired, female terrier, weighing 9.4 kilos, while under morphin was given three deep breaths of the concentrated gas. The animal was very dyspneic for a few minutes and then became active and apparently suffered no discomfort. Six days afterward it was coughing a good deal. One month later it was apparently entirely well and healthy, and was then put under the influence of morphin and given two exposures to nitrogen tetroxid fumes, about two hours apart. The day following the animal appeared very sick and refused to eat or drink. Râles in throat and difficult breathing. Two days later it was still coughing up a white mucous sputum. The animal was very quiet and refused to eat. Five days later it was killed. The lungs were very voluminous. There were firm sunken areas along the borders of the posterior portions of the lobes. These areas were of a grayish color. The bronchi protruded from the surface of the cut lung and contained a mucopurulent fluid. The solid lung tissue was greenish-gray in color. The bronchi in some portions of the lung were very much dilated. The microscopic changes in the lungs were about the same as in Dog 4, but there was much more emphysema and the bronchi were more extensively altered and dilated. The second exposure evidently extended these changes in an already diseased lung.

Dog 13—Short-haired terrier, weighing 8.5 kilos. Under morphin the animal was given several deep breaths of well diluted nitrogen tetroxid. It recovered and at the end of a month was apparently well, but finally began to cough and lose weight, and was killed five weeks after exposure. During the last few days the animal coughed a good deal. At autopsy a lobular bronchopneumonia was found together with the usual emphysema. An atypical pneumococcus was isolated from the pneumonic areas, and the lesion, when examined microscopically, was found to be quite different from that seen in the other dogs, corresponding to that found after bacterial infections. The alveoli were filled with a richly leukocytic exudate, and bacteria could be demonstrated by appropriate stains. The lesion was evidently a spontaneous bacterial pneumonia developing in a lung weakened by the action of the nitrogen tetroxid fumes. Such a pneumonia is not infrequent in animals on whom severe operations have been performed.

#### PROPHYLAXIS

The chief danger of nitrogen tetroxid lies in the fact that a 1 per cent mixture of the gas with air can be inhaled without inducing coughing or spasm of the larynx, so that the bronchial and pulmonary epithelium is seriously damaged before severe symptoms supervene. This is quite impossible with chlorine, sulphur dioxide, or ammonia, which cannot be inhaled even in a mixture much diluted with air without causing a spasm of the glottis and suffocation.

As the gas is generated by contact of nitric acid with any organic matter, the straw packing and wooden cases in which the acid carboys are inclosed usually start the reaction, the heat evolved often being sufficient to set the woodwork on fire, thus increasing the difficulty of handling the situation. Nitric acid should, therefore, be stored in an amply ventilated separate building with stone or concrete floor, if possible, and arrangements should be made so that the room can be promptly flooded with water. The handling of the carboys should be

placed in the hands of a few skilled workmen who have been instructed as to the dangers of inhaling the fumes arising when the acid is spilled. Sand is the best material for absorbing any acid which may be upset. If it is necessary for the workmen to enter a room in which the acid has been spilled, their mouths and noses should be covered with cloth moistened with very dilute ammonia.

#### TREATMENT

There is no satisfactory treatment after the gas has been inhaled. Breathing ammonia vapor has been suggested, but this only adds a second corrosive gas to that already present in the lungs. Oxygen inhalations aid in combating the dyspnea, but do not touch the cause of this symptom, which is chiefly due to the edema of the walls of the bronchi. Morphine and stimulants should be given according to the symptoms.

#### CONCLUSIONS

1 The inhalation of even small quantities of nitrogen tetroxide gives rise to an exceedingly dangerous pulmonary condition with a characteristic lung lesion both in man and in animals.

2 As there is no satisfactory treatment of the condition it is of the utmost importance that careful instruction be given to all factory laborers or laboratory workers who have to handle concentrated nitric acid as to the dangers incurred and the means of avoiding them.

#### BIBLIOGRAPHY

An excellent description of the symptoms in poisoning by nitrogen tetroxide with a fair bibliography is to be found in Kunkel, *Handbuch der Toxikologie*, Jena, 1901, p. 282. Pott (*loc cit*, note 24) gives references to the older cases. Robert, *Lehrbuch d. Intoxikation*, 1906, also gives a considerable number of references to the literature, not without the usual inaccuracies. Kockel (*loc cit*, note 13) refers to a number of recent cases, and Schubert (*loc cit*, note 7) has a fair bibliography and gives important suggestions for prophylaxis. The best bibliography is contained in Witthus and Becker, *Medical Jurisprudence and Toxicology*, 1911, iv, 301, New York.

# ORGANIC IODIN PREPARATIONS, THEIR PHARMACOLOGY AND THERAPEUTIC VALUE

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The introduction within recent years of numerous organic iodin compounds as substitutes for the iodids, the extravagant claims made for some of them by the manufacturers, both as regards therapeutic efficiency and absence of toxic side actions, and the scarcity of literature on the subject in American periodicals seem to demand a review of the entire subject of the value of these substances as therapeutic agents. Most of these compounds have originated from German manufacturers, and nearly all of the investigations regarding them have been published in that country. These substances, however, are being rapidly introduced into the American market, and at the suggestion of the Council on Pharmacy and Chemistry of the American Medical Association, I have undertaken an investigation of the pharmacological basis for the use of such compounds as substitutes for the iodids. The present paper deals chiefly with the literature on the subject.

## I—CLASSIFICATION AND CHEMICAL NATURE

Most of the organic iodin preparations introduced up to the present time as substitutes for inorganic iodids are addition products of iodin with either proteins or unsaturated fatty acids or fats. Other organic combinations of iodin have usually so great an action due to the remainder of the molecule that the iodin action is obscured, and they are as a rule not suitable for administration as substitutes for the iodids.

A *Iodized Albumins or Proteins*—The first iodized albumins were prepared by Boehm and Berg.<sup>1</sup> The resulting product could be easily deprived of its iodin by washing with water, or by dialysis, so that the combination between the iodin and the albumin was not firm, and they considered that the iodin was mechanically held. Liebrecht and Roehmann<sup>2</sup> iodized casein by warming it with iodin. The resultant compound contained no free iodin, but gave off iodin on washing with water and alkalis. Then "Periodcasein" held 17.8 per cent of iodin, but after washing it left "Iodecasein" with 5.7 per cent. Both compounds split off sulphur and phosphorus easily. Hofmeister<sup>3</sup> prepared iodo-albumin from

<sup>1</sup> From the Laboratory of biochemistry and pharmacology, University of Chicago.

<sup>2</sup> Submitted for publication Sept. 17, 1912.

<sup>3</sup> Investigation supported by a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association.

<sup>1</sup> Boehm and Berg, *Arch f exper Path* 1876, 1, 329.

<sup>2</sup> Liebrecht and Roehmann, *Arch f exper Path* 1894, xxx, 1824.

<sup>3</sup> Hofmeister, *Ztschr f physiol Chem* 1897, xxx, 159.

crystallized egg albumin. Many other iodized proteins are now on the market, and several of them are described below. Most of these preparations no longer give the Millon reaction, and on this account it has been considered that the tyrosin group in the protein molecule has taken up the iodine. To bear this out, a tyrosin-iodine compound (3-5 diiodotyrosin, an iodine complex found in sponges<sup>4</sup> and other places in nature) has been separated from a number of the iodized proteins by hydrolysis (*vide infra*). Undoubtedly, however, as shown by Oswald<sup>5</sup> and by Pauly,<sup>6</sup> other groups in the protein molecule are also involved in the combination, and according to their work it is probable that both histidin and phenylalanin may take up iodine when a protein is iodized. It has been shown that many of the commercial preparations of iodized proteins consist of a mixture of a true compound of iodine with the protein molecule, of inorganic iodide, possibly loosely combined, and in some cases, of free iodine. The nature of the commercial preparations of iodized proteins so far studied may be here briefly summarized. Many of these preparations are not yet on the American market.

#### COMMERCIAL PREPARATIONS

*Iodalbacid* (Fabrikanten Herin Gans in Frankfurt) is a commercial iodized albumin, said to be obtained by electrolyzing an iodide solution in which the anode is surrounded by a protein. It is said to contain 10 per cent of iodine. Oswald<sup>7</sup> hydrolyzed this compound and obtained 0.4 gram of diiodotyrosin from 100 grams original substance. Taege<sup>8</sup> also examined this substance and found it to contain only 5.5 to 5.6 per cent of iodine. He found it free of inorganic iodine, and found no iodine split off on shaking with water, and concluded that all the iodine is bound in the molecule. When given by mouth he found that 66 per cent of the iodine was excreted in the urine within eighty hours, 60 per cent in organic combination and 6 per cent in inorganic form.

*Iodized egg white* is manufactured in three forms (Chem. Fabrik von Dieterich in Helfenberg). (1) *Iodeigon* is an iodized, water insoluble, egg albumin, with 20 per cent of iodine. This compound was studied by Taege,<sup>8</sup> who found that 95 per cent of the total iodine was in loosely combined, inorganic form, mainly as hydriodic acid, and this was easily split off on shaking with cold water. On giving this compound by mouth he found that the excretion ended in ninety hours, with the excretion of 76.4 per cent of the total iodine, with 23.4 per cent in organic form and 53.0 per cent in inorganic form. (2) *Iodeigonatrium* is a

4 Wheeler and Mendel Jour Biol Chem, 1909, vii, 1

5 Oswald Ztschr f physiol Chem, 1909, lvi, 299

6 Pauly Ztschr f physiol Chem, xliii, 2243

7 Oswald Ztschr f physiol Chem, 1911, lxx, 311

8 Taege Med Klin, 1910, vi, 1536

water soluble, sodium salt of an iodized egg albumin, said to contain 15 per cent of iodin. This compound was examined by Oswald,<sup>9</sup> who found 96 per cent of the iodin split off after four and one-half hours boiling with saturated barium hydrate. He was unable to separate iodotyrosin from this substance. Mosse and Neuberg<sup>10</sup> also examined this compound and found only a little iodin split off on boiling with dilute acids. (3) *Peptoiderigon* (iodopeptone), a third form, contains 15 per cent of iodin. *Iodomangan*, N N R, contains 1 per cent of this compound.

*Iodglidin* (Klopfer, in Dresden) is an iodized plant albumin (gliadin) containing 10 per cent. of iodin, of which 38.4 per cent is in loosely combined, inorganic form (Taege). Taege gave this compound by mouth and found 63.2 per cent of the iodin excreted in seventy-eight hours, with 48.2 per cent in inorganic form and 15 per cent in organic combination. Neuberg<sup>11</sup> hydrolyzed this compound with 30 per cent sulphuric acid at 40 C, and separated a crystalline copper salt containing 52.25 per cent iodin, but he did not obtain diiodotyrosin. Oswald<sup>7</sup> also hydrolyzed iodoglidin and obtained 7.3 per cent of the original iodin present as diiodotyrosin, using saturated barium hydrate as the hydrolyzing agent. Wheeler and Mendel<sup>12</sup> also found diiodotyrosin on hydrolysis. According to Broking,<sup>13</sup> iodoglidin is very unstable, affected by light, pepsin, trypsin, etc. The iodin is firmly combined only in part, and a much greater part is loosely held, this agreeing with the results of Taege. Boruttau<sup>14</sup> showed that iodin could be split off by digestion with pepsin, treating with alcohol, or boiling with acids.

*Iodalbin*, N N R (Parke, Davis & Co.), is said to be a compound of iodin with blood albumin, containing approximately 21.5 per cent of iodin. It is said to contain no free iodin, unless decomposed. It is insoluble in the ordinary solvents, but soluble in alkalies. I have examined samples of this substance, obtained in the open market, and find the claims as to the total amount of iodin to be substantiated, as I have found 21.6 per cent of iodin. The dry substance gives a strong blue color with starch paste. On shaking for a few minutes with a dilute solution of potassium iodid (6 gm. in 500 c.c.) an amount of iodin equivalent to 3.1 per cent of the original weight of the substance is separated from it. On shaking for four hours in distilled water, at room temperature I have found an amount of iodin equivalent to 4.9 per cent of the original weight of the substance to be separated off. The considerable amount of

<sup>9</sup> Oswald. *Ztschr. f. physiol. Chem.*, 1911, LXIII, 374.

<sup>10</sup> Mosse and Neuberg. *Ztschr. f. physiol. Chem.*, 1902-3, XXXVII, 427.

<sup>11</sup> Neuberg. *Biochem. Ztschr.*, XXIII, 251.

<sup>12</sup> Wheeler and Mendel. *Biochem. Ztschr.*, 1910, XXIV, 419.

<sup>13</sup> Broking. *Ztschr. f. exper. Path.*, 1910, VIII, 125.

<sup>14</sup> Boruttau. *Dtsch. med. Wchnschr.*, 1907, 1490.



free iodin which the substance contains would doubtless prove irritating in the stomach

*Iodomenin* (Herr Wolfing, Berlin) is a compound of albumin with the bismuth iodine. It contains 4.45 per cent of iodine (Taege<sup>8</sup>), and of this 94.4 per cent is split off by shaking with water, most of it being united to bismuth. Taege gave this substance by mouth, and found 81.4 per cent of the total iodine given, excreted in ninety hours, 65.7 per cent inorganic, and 15.7 per cent inorganic combination.

*Proiodin* (Wolf, in Bielefeld) is an iodized casein with an iodine content of 4.23 per cent (Taege<sup>8</sup>), that is firmly bound in the protein molecule. Practically all of this substance is excreted in organic combination.

*Iodomarsine* is the iodized product of the albumin from corn meal (zein) containing 44.68 per cent of iodine. It gives both the biuret and Millon reactions.

*Iodtropin* (Troponwerken in Mulheim) contains 5 per cent of iodine. Of the total iodine only 3.37 per cent is split off on shaking with cold water, leaving 96.63 per cent in organic combination. In sixty hours only 13.2 per cent of total iodine given was found in the urine (Taege<sup>8</sup>), and at that time the urine was free of iodine.

B. *Iodized Fats and Fatty Acids*—The first iodized fat to be recommended for therapeutic use was described by Winternitz<sup>15</sup>. It was introduced into the market under the name of *Iodipin* (*vide infra*). Since then numerous other compounds have been manufactured, their composition depending on the fact that the free valences in unsaturated fatty acids may be satisfied by iodine. The resulting compounds are generally free from free iodine, and do not yield their iodine readily, except on hydrolysis. They are generally, therefore, more stable than the iodized albumins.

*Iodipin*, N N R (Merck), is the product of the addition of iodine chloride to oil of sesame. It is on the market in two forms, one of 10 per cent strength, and the other of 25 per cent strength, for hypodermic use. The darker color of the 25 per cent preparation is not due to free iodine, but to a resin-like body which the oil contains<sup>16</sup>.

*Sajodin*, N N R (Farbenfabriken von Elberfeld), is the calcium soap of a fatty acid obtained by iodizing erucic acid, forming iodo-behenic acid. The formula is said to be  $(C_{21}H_{42}IOO)_2Ca$ . Theoretically this should contain 26.03 per cent of iodine. Two samples analyzed by me showed an iodine content of 22.46 per cent and 22.58 per cent. On boiling for fifteen minutes with 25 per cent sulphuric acid, the substance splits off the iodized fatty acid, which by further hydrolysis yields its iodine.

15 Winternitz. *Deutsch med Wehnschr*, 1897, *xviii*, 477.

16 Winternitz. *Munchen med Wehnschr*, 1903 *i*, 1241.

*Lipoidin* is a new iodized fatty acid ester described by Loeb and van der Velden<sup>17</sup> It is the ethyl ester of a diiodized, unsaturated fatty acid of the formula  $C_{24}H_{44}I_2O_2$ , containing 41.06 per cent of iodine It is soluble in 70 per cent alcohol, also in oils, fats, benzol, chloroform, and insoluble in water

*Iodostarin* (Hoffmann-La Roche Chemical Works) is a new diiodized fatty acid of the formula  $C_{18}H_{22}I_2O_2$ , and should contain 47.5 per cent of iodine The Hoffmann-La Roche company has furnished me with sample tablets of the substance, each containing 0.25 grams of the compound, and said to contain 0.12 grams of iodine In my analysis of these tablets I have found the iodine content to be 46.53 per cent, each tablet containing 0.116 grams Iodostarin occurs as a colorless powder, insoluble in water, but soluble in alcohol, ether, etc

*Iodival* (Knoll & Co) is iodoisovalerianyl urea, corresponding to the bromide compound "Biomural," N N R It is somewhat soluble in water It is said to contain 47 per cent of iodine

C *Other Organic Iodine Compounds*—The other organic iodine compounds used therapeutically are used mainly for their antiseptic action Iodoform ( $CHI_3$ ) has, of course, priority over the rest of these Numerous substitutes for iodoform have been introduced, such as *Thymol Iodide*, U S P (Aristol), *Europhen*, N N R, *Avol*, N N R, *Iodone*, N N R, *Iodoformogen*, N N R, *Vioform*, N. N. R, etc If these substances are given internally they are split in the body, and the iodine is liberated in the form of iodides, and excreted, but the substances themselves and their decomposition products in the body have certain toxic actions (such as that of iodoform) which render them unsuited for internal use.

*Iothol*, N N R (Farbenfabriken von Elberfeld Co), is di-iodo-hydroxy-propane, obtained by chlorinating glycerin and replacing the chlorine by iodine It is a yellowish, oily, heavy liquid, said to contain 77 per cent of iodine, and is recommended for application to the skin in the form ofunctions, for absorption

*Glycerodin*, N N R (H K Wampole), the glycerite of hydriodic acid, is not a true organic preparation

*Iodocitin* is a recently described compound of iodine and lecithin<sup>18</sup>

## II—ABSORPTION AND EXCRETION

Since most of the organic iodine preparations used internally are addition products of iodine with proteins or fatty acids, the question of their absorption is intimately concerned with the physiology of the

<sup>17</sup> Loeb and Van der Velden *Therap Monatsh* 1911, xxv, 209

<sup>18</sup> Neuberg *Therap d Gegenw*, August, 1911.

absorption of the proteins and fats. As certain changes occur in these substances in the process of digestion and absorption, we expect to find that their iodine addition products will undergo certain similar changes in the gastro-intestinal tract. Boruttau<sup>19</sup> has carried on artificial peptic and pancreatic digestion of the iodized proteins, and has determined the amount of iodine present in the splitting products obtained. He found that the compounds which are easily deprived of their iodine by washing, etc (such as iodoglucine), yield it readily on digestion, and a relatively large amount appears as inorganic iodide, while a relatively small amount remains in the undigested residue. The reverse is true of the more stable compounds, such as iodalbumin. He found iodine in all the fractions of acid proteins, peptones, etc. He concluded that the splitting off of inorganic iodine did not occur in the stomach, though it could be produced outside the body by peptic digestion, but that the splitting products of the proteins left the stomach before that stage had been reached, and that the process was completed by pancreatic digestion, and that a large amount of the iodine was absorbed in the form of inorganic iodides. V. Furth and Friedman<sup>20</sup> demonstrated that when iodalbumin, one of the more stable compounds, was fed, most of the iodine was carried in the blood in inorganic form. Some absorption of the iodine in the form of iodized splitting products of the proteins also occurs, the amount depending on the amount of iodine which is firmly bound in the protein molecule. As 3-5 diiodotyrosine has been obtained from hydrolysis of many of the iodized proteins, it is probable that a part of the iodine is absorbed in that form, and similar forms. Mosse and Neuberg<sup>21</sup> found iodhippuric acid in the urine on feeding iodigonatium to rabbits, and found iodbenzoic acid in the blood on feeding the same substance to dogs. Oswald<sup>22</sup> was unable to confirm their results, and concludes that the iodine in the preparation used was not held as diiodotyrosine.

The form in which the iodine, fed in the form of iodized proteins, is excreted depends largely on the form in which it is absorbed. Taege<sup>8</sup> has shown a close parallelism to exist between the stability of the iodized proteins and the amount of organic iodine in the urine. It is probable, therefore, that a large part of the iodine absorbed in organic combination is excreted in practically the same form, without ever being liberated in inorganic form. This is borne out by the work of Oswald,<sup>23</sup> who fed 3-5 diiodotyrosine to rabbits, and found that about half of the iodine given was

19 Boruttau. *Ztschr f exper Path u Therap*, 1910, viii, 418.

20 Von Furth and Friedman. *Arch f exper Path, Festschr f Schmiedeberg*, 1908, p. 214.

21 Mosse and Neuberg. *Ztschr f physiol Chem*, 1903, xxviii, 419.

22 Oswald. *Ztschr f physiol Chem*, 1910, lxx, 141.

23 Oswald. *Ztschr f physiol Chem*, 1909, lvi, 399.

excreted in the urine in organic combination, partly in the same form in which it was given. This iodine would necessarily, therefore, be devoid of any iodine "ion action." Abderhalden and Slavu<sup>24</sup> gave 3-5 diiodotyrosine by mouth and subcutaneously and found most of the iodine in the urine in inorganic form. They found some in organic combination, but not as diiodotyrosine. They found, however, a considerable amount of diiodotyrosine in the feces, even when the substance was given subcutaneously.

The fate of the iodized fats is similar to that of the fats and fatty acids themselves. They generally pass through the stomach unchanged<sup>25</sup> and are split in the intestines and absorbed. In the case of sajodine, the calcium is probably first split off, as this change occurs first on hydrolysis, and following this there is at least partial splitting off of the iodine from fatty acid. Metzger<sup>26</sup> fed sajodine to dogs with intestinal fistulæ, and showed the presence of inorganic iodine in the duodenum during digestion. With iodipin he was unable to demonstrate any inorganic iodine in the stomach or upper duodenum. According to Winternitz,<sup>16</sup> iodipin is not absorbed in the stomach, but is split in the intestines by the bile and pancreatic and intestinal juices, leaving the iodine bound to the fatty acid, and is absorbed mainly as the iodized fatty acid. He showed that the iodine was present in the ether extract of the blood after absorption, and concluded that it was identified with the fats there. By oxidation of the iodized fatty acid in the blood and in the tissues the iodine is split off in the form of iodide and excreted. Wells<sup>27</sup> concluded that when iodipin was injected subcutaneously it was carried in the blood mainly as inorganic iodine. Boruttau<sup>19</sup> gave sajodine and iodival in large doses to dogs, took blood from the carotid, and found that much more iodine was present in the blood in inorganic than in an organic form. Abderhalden and Kautzsch<sup>28</sup> concluded that sajodine was absorbed as the mono-iodobehenic acid, and was taken into the cells in that form, and that iodine was liberated by oxidation in the cells. My analysis of the liver after giving sajodine (*vide infra*) would indicate that a part of the iodine is present in the tissues as the iodized fatty acids, though I do not regard this as sufficiently demonstrated.

Loeb and van der Velden<sup>17</sup> showed that iodival is absorbed without any inorganic iodine being split off in the intestine. Broking<sup>13</sup> came to the same conclusion.

24 Abderhalden and Slavu. *Ztschr f physiol Chem*, 1909, lxi, 405

25 Posternak. *Bull Soc de therap. series 4*, 1910, xi, *Bachem Munchen med. Wehnschr*, 1911, No 41

26 Metzger. *Med Klin*, 1911, vii, 1390

27 Wells. *Ztschr f physiol Chem* 1905, xlv, 412

28 Abderhalden and Kautzsch. *Ztschr f exper Path u Therap*, 1907, iv, 1.

When the iodized fats are taken the greatest amount of iodine leaves the body in the urine in the form of potassium iodide,<sup>29</sup> though a small amount is present in the urine in organic combination. This is of no significance, as about 99 per cent of iodine given as potassium iodide may appear in the urine in organic combination (Taege<sup>8</sup>), and Harnack<sup>30</sup> has shown that a spontaneous change from iodide to organically combined iodine may occur under normal circumstances in fresh urine.

The excretion of iodine in the milk, when given in the form of iodized fats, is of interest. Lons<sup>31</sup> fed lipiodine and found greater amounts of iodine in the milk than when corresponding amounts of potassium iodide were fed. He was unable, however, to identify the iodine in the milk with the milk fat. Winternitz<sup>15</sup> fed iodized hog fat to a goat, and found iodine in the milk in the form of an iodized milk-fat, and also in the milk serum in inorganic form. In seven days 62 per cent of iodine given was excreted in the form of iodized milk-fat.

The absorption of iodine compounds from other places than the gastrointestinal tract has been studied. The absorption of iodine when administered subcutaneously has already been mentioned. Winternitz<sup>16</sup> showed that iodine was not absorbed through the unbroken skin, as the urine remained iodine-free, and he also showed that not over 10 per cent was absorbed when administered by rectum. Iothion, which is of the nature of an iodized volatile oil, is rapidly absorbed through the unbroken skin,<sup>32</sup> appearing in the urine in about one hour. It is irritant to the skin, and is usually applied in the form of an emulsion, using lanolin as a base.

#### RATE OF ABSORPTION AND EXCRETION

The rate of absorption and excretion of the organic iodine preparations has been studied mainly in comparison with the excretion of potassium iodide. The excretion of potassium iodide has been studied by many observers, and the results agree in general with those of Anten,<sup>33</sup> who showed that (1) after one dose of potassium iodide (0.5 grams) the highest amount in the urine is in the second hour, rarely in the first or third, (2) the average amount excreted in the urine after this dose is 75 per cent (minimum, 65 per cent, maximum, 85 per cent), (3) the duration of the presence of iodine in the urine after such a dose of 0.5 grams is forty hours. After two doses five hours apart the duration is fifty-six hours, and after three doses in ten hours is seventy-seven hours, (4) when mucilaginous bodies are given with potassium iodide the excre-

29 v Klingmüller *Beil klin Wehnschr*, 1899, p. 540, Winternitz *München med Wehnschr*, 1903, I, 1241.

30 Harnack *Arch internat d Pharm u Therap*, 1910, II, 247.

31 Lons *Berl klin Wehnschr*, 1911, XLIII, 2064.

32 Kellermann *Ztschr f exper Path*, 1905, II, 416.

33 Anten *Arch f exper Path u Pharm*, 1902, XLIII, 331.

tion is slower in the first two hours, (5) when potassium nitrate or sodium chlorid is given with potassium iodid the excretion of iodine is distinctly greater. Brooking<sup>13</sup> found potassium iodid to be rapidly absorbed in the small intestine and the excretion in the urine to average 80 per cent of that given. Excretion begins a few minutes after taking, and lasts in the urine sixty hours as a maximum. He found 75 per cent excreted in the urine in the first twelve hours, and only 5 per cent after that time, and found iodine in the feces only in traces. The relation between the excretion of chlorine and iodine, and particularly between chlorine and bromine has been studied by a number of observers. Sarvonat and Crenieu<sup>34</sup> have shown that animals on a chlorine free diet retain iodine in the tissues longer and in greater amounts than those receiving chlorides in the diet. The fate of the iodine which does not appear in the urine has not been entirely settled. Only small amounts appear in the feces, but iodine has been found in the perspiration, and in the hair, etc., and the thyroid may hold a considerable amount (*vide infra*). Boruttau<sup>19</sup> found small amounts in the intestine, kidneys, heart and lungs four days after giving potassium iodid to a rabbit.

The iodized fats and fatty acids show the greatest difference from potassium iodid with regard to rapidity of excretion. After the administration of sajodin the iodine does not appear in the saliva and urine until after one to three hours, and eighty-four hours is required for excretion of iodine in the urine after a single dose, during which time 35 to 50 per cent of iodine given appears in the urine (Brooking<sup>13</sup>). From 7 to 10 per cent appears in the feces unchanged. The highest point in the excretion is reached in the first twelve hours, but the amount excreted remains high during the first thirty-six hours, though in the case of potassium iodid it falls very low after twelve hours. Singer<sup>35</sup> found only 58.5 per cent of iodine given as iodipin in the urine, and showed that the excretion was much slower than in the case of potassium iodid. Brooking<sup>13</sup> showed that the excretion of iodival began rapidly, reached its height within a few hours, and continued about sixty hours after a single dose, resulting in the excretion of about 80 per cent of the iodine given. He showed that the rate of excretion was somewhat more uniform than with potassium iodid especially when the drug was given in successive doses. He found 2 per cent remaining in the feces. Loeb and van der Velden<sup>17</sup> showed that iodival is rapidly absorbed and appears in saliva and urine in twelve minutes, and that the rate of excretion is practically parallel with potassium iodid. Loeb and van der Velden also showed that with lipiodin the excretion began in two to three hours, and continued seventy-two to 120 hours, and they found an average of 3 to 12 per cent in the

34 Sarvonat and Crenieu. *Compt rend Soc de biol*, 1911, lxx, 268

35 Singer. *Ztschr f klin Med* 1904 lii, 521

feces under normal conditions. They also found some of the iodine present in the blood in ether-soluble form, and concluded that the ester or the free fatty acid was absorbed with iodine combined. Abderhalden and Hirsch<sup>36</sup> found that the ethyl esters of iodized fatty acids, such as lipiodine, were slowly absorbed. Loeb and van der Velden concluded that when lipiodine was given the iodine was slowly and evenly split off, giving a comparatively even iodine effect.

The iodized proteins, being of a more or less unstable character, are generally absorbed and excreted more rapidly than the iodized fatty acids, and the rate of excretion is more nearly like that of potassium iodide. Brooking<sup>13</sup> found iodoglucine to be excreted in a similar manner to iodine, and found 3 to 4 per cent in the feces. I have found iodine in the urine within fifteen minutes after the administration of iodalbumin, which would be expected from its content of free iodine. The work of Taege, showing the relationship between the stability of the iodized proteins, has already been quoted (*vide supra*).

Metzger<sup>26</sup> studied the excretion of iodocitin (iodized lecithin) and found the highest point in excretion within the first twelve hours, a considerable amount being excreted in organic form.

The relation between iodine and chlorine excretion has been shown by Herzfeld and Heiman<sup>37</sup> to be the same in the case of iodostarin as when the iodides are given.

The influence of pathological conditions on the absorption and excretion of certain compounds has been studied by Loeb and van der Velden,<sup>17</sup> who showed that in patients with diarrhea, 50 per cent of iodine given as lipiodine may appear in the feces. Van der Velden<sup>38</sup> found that the excretion of iodine in the urine may be markedly changed from normal under certain pathological conditions. He found that there was a slowed excretion of potassium iodide, but a quickened excretion of iodine, and concluded that there may be a more rapid and intensive splitting of the iodine from the organic complex in the one case. The lessened excretion of iodine in nephritis has also been shown in the case of iodine by Norsa and Arcadi<sup>39</sup>.

### III—DISTRIBUTION IN THE BODY

The factors concerned in the entrance of the various iodine compounds into the cell are still unsettled. O. Loeb<sup>40</sup> gave potassium iodide to rabbits, and found the largest amounts of iodine in the blood, kidneys and lymph-nodes (exclusive of thyroid). He found the brain, spinal cord, fatty tissues and bone always iodine-free. When he gave iodine, iodanilin and

36 Abderhalden and Hirsch. *Ztschr f physiol Chem*, 1911, lxxv, 38.

37 Herzfeld and Heiman. *Med Klin*, 1911, vii, 1858.

38 Van der Velden. *Therap Monatsh*, 1910, xiv, 632.

39 Norsa and Arcadi. *Zentralbl f Biochem*, v, 619.

40 Loeb, O. *Arch f exper Path*, 1907, lvi, 310.

iodoform he found iodine in the brain and in fatty tissues, and he ascribed their entrance into these tissues to their lipid solubility. Boruttau<sup>40</sup> was unable to confirm his results with regard to potassium iodide, as he found iodine in the brain after giving potassium iodide. Boruttau found, four days after giving iodized proteins, that the largest amounts of iodine were in the brain. He concludes that the "Neurotropie" and "Lipotropie" of Loeb are relatively unimportant, except for iodized fats subcutaneously injected.

In this connection it is important to know in what form the iodine is present in the tissues. Lesser<sup>41</sup> gave a rabbit 10 c c of 25 per cent iodipin within twenty-four days, separated the fats from the tissues by ether extraction and obtained the following results:

Organ	Weight	— Mg per Gram of Organ —	
		Total Iodine	I as Iodized Fat
Lung	26.4	0.55	0.255
Liver	68.0	0.45	0.1
Kidneys	18.2	0.2	0.009
Mesenteric fat	4.0		0.045
Blood	100 c c	0.15	trace

He concluded that on giving iodized fat a large amount of iodine was split off, and only a part circulated in the blood as fat or fatty acid, while a part is taken up by the tissues in the form of the fat or fatty acid.

To determine with what constituents of the cell the iodine is mainly identified after entrance into the tissues, I have analyzed certain tissues for the distribution of iodine in the cell, after giving iodized fatty acids, iodized proteins and potassium iodide. The liver was chosen for this work, as it is of convenient size (in rabbits) for extraction, and because it contains a considerable amount of lipid substance, and also because it takes up a considerable amount of iodine. The separation of the cell constituents was made by the method described by W. Koch<sup>42</sup>. The rabbits were given the iodine compound hypodermically or by stomach tube, and were later killed by bleeding from the neck, and the tissues collected and estimations of the total iodine in the principal organs made. The liver was cut up in small pieces and put in enough absolute alcohol to make 85 per cent alcohol, with the water in the tissue, and allowed to stand for one to two weeks, after heating up to 70°C for about an hour. It was then subjected to a continuous hot alcohol extraction in the extraction apparatus described by Koch, for four hours, followed by an ether extraction of one hour. The dried residue was then finely powdered, soaked up with water, made up again with absolute alcohol to 85 per cent alcohol and allowed to stand a few hours, after which it was again extracted with hot alcohol for about twelve hours. The residue was then dried in

<sup>41</sup> Lesser Arch f Dermatol Syph, 1903, lxxv, No 1

<sup>42</sup> Koch W Jour of Am Chem Soc, 1909, xxxi, 1330



an oven to constant weight. The alcohol extract was evaporated to near dryness, dried for two to three days in a vacuum desiccator and emulsified in water. After complete emulsification the lipoids were precipitated according to the method of Koch,<sup>42</sup> by hydrochloric acid and chloroform. Estimations were made of the amount of iodine in the three fractions separated in this way: (1) protein residue, (2) lipoids—alcohol soluble, water insoluble, (3) water soluble, alcohol soluble. All iodine determinations were made by a slight modification of the method described by Hunter.<sup>43</sup> This method has given very uniform results in our hands.

The protocols of typical experiments will serve to illustrate the results.

*Experiment V—Potassium Iodide—Rabbit, weight 1,600 gm*

July 22, 3 p m, 0.8 gm KI in water by stomach tube

July 23, 9 a m, 0.5 gm KI in water by stomach tube

July 23, 10 30 a m, killed by bleeding from neck

*Analysis of Tissues*

Organ	Weight, Fresh, gm	Mg I per Gram Fresh Tissue
Kidneys	10.1	0.344
Blood	47.1	0.292
Heart	4.15	0.122
Liver	65.95	
Protein residue		0.000
Lipoid (alc sol, water insol)		0.032 (32.0%)
Alcohol soluble, water sol		0.067 (67.0%)
Total		0.099
Brain	8.95	0.007

*Experiment VI—Iodalbumin—Rabbit, weight 1,600 gm*

July 25, 3 00 p m, 2 gm iodalbumin in NaHCO<sub>3</sub> sol by stomach tube

July 26, 11 45 a m, 2 gm iodalbumin in NaHCO<sub>3</sub> sol by stomach tube

July 26, 2 00 p m, killed by bleeding from neck

*Analysis of Tissues*

Organ	Weight, Fresh, gm	Mg I per Gram Fresh Tissue
Kidneys	9.7	0.21
Blood	63.7	0.209
Heart	4.0	0.116
Liver	70.45	
Protein residue		0.000
Lipoid (alc sol, water insol)		0.014 (24.5%)
Alcohol sol, water sol		0.043 (75.4%)
Total		0.057
Brain	8.25	0.008

*Experiment II—Sajodin—Rabbit, weight 1,790 gm*

June 24, 0.3 gm sajodin in olive oil subcutaneously

June 25, 0.3 gm sajodin in olive oil subcutaneously

June 26, 9 30 a m, 0.5 gm sajodin in olive oil subcutaneously

June 26, 1 30 p m, killed by bleeding from neck

<sup>43</sup> Hunter Jour Biol Chem, 1910, vii, 321

*Analysis of Tissues*

Organ	Weight, Fresh, gm	Mg I per Gram Fresh Tissue
Heart	4 6	0 0276
Kidneys	10 82	0 0257
Lungs	9 12	0 0185
Liver	54 9	
Protein residue		0 0000
Lipoid (alc sol, water insol)		0 0106 (62 7%)
Alcohol sol, water sol		0 0063 (37 3%)
Total		0 0169
Blood	74 7	0 0151
Spinal cord	2 7	0 0078
Brain	7 85	0 0053

*Experiment IV*—Sajodin—Rabbit, weight 1,400 gm

July 17, 2 10 p m, 2 gm sajodin in olive oil by stomach tube

July 18, 9 30 a m, 2 gm sajodin in olive oil by stomach tube

July 18, 1 30 p m, killed by bleeding from neck

*Analysis of Tissues*

Organ	Weight, Fresh, gm	Mg I per Gram Fresh Tissue
Heart	3 2	0 178
Liver	49 5	
Protein residue		0 010 ( 6 4%)
Lipoid (alc sol, water insol)		0 082 (52 9%)
Alcohol sol, water sol		0 063 (40 6%)
Total		0 155
Blood	26 5	0 125
Kidneys	8 3	0 102
Brain	6 05	0 026

The results of these experiments would tend to show the following.

1 There are no essential differences in the distribution of iodid after giving potassium iodid and iodalbum, either in the distribution between the different organs, or in the distribution in the various constituents of the cell

2 Sajodin produces a relatively higher percentage of iodin in the lipid fraction, indicating that the lipoids of the cell take up iodized fats from the blood (More data are required on this point)

3 The relative amount of iodin in the nervous tissues after sajodin is much greater than after potassium iodid or iodalbum—though small amounts of iodin have been found in all cases The liver also stands relatively higher in iodin content after sajodin

## IV—PHYSIOLOGICAL ACTION

The question of the physiological action of the organic iodin preparations is even more complex than that of the inorganic iodids, about which we know relatively little In the case of potassium iodid, we have to consider the action of the salt itself, its ions after dissociation, and the free iodin which may be liberated in the body In the case of an iodized

fat or protein we must consider the action of the molecule as a whole, its organic splitting products, the action of the iodine after liberation from the molecule and recombination in organic or inorganic form in the body. The last-named action would probably be identical with the action of iodine given in inorganic form. O. Loeb<sup>44</sup> divides the consideration of iodine action into three groups: (1) salt action, (2) effects on physiologic activity of thyroid and (3) changes produced in pathologic conditions. He assumes that iodism is due to the flooding of the organism with iodine ions by rapid absorption of potassium iodide, and advocates the use of iodized fats (lipiodin) since the iodine is gradually split off and "flooding" is avoided.

Erlenmeyer and Stein<sup>45</sup> conclude that all iodine action is ion action, that organic iodine compounds act only as iodine is split off in the body, and that such substances as iodipin and sajodin, by their smaller iodine content, are weak substitutes for potassium iodide. They regard iodism as an undesirable side action of ion action. Winternitz,<sup>46</sup> however, maintains that it has not been shown that the action of all iodine preparations is due entirely to ion action, or that iodipin and sajodin must be changed into potassium iodide to act, and he claims that iodism is much less frequent with the iodized fats. His contention is undoubtedly true, in that we may have other actions from iodized fats than the iodine ion action, but we have no evidence that the action so produced is the action desired in the cases in which the drugs are recommended as substitutes for potassium iodide.

With regard to the question of iodism, v. Notthafft<sup>47</sup> concluded that the diminution in frequency of observation of iodism with the organic iodine preparations was always associated with other disadvantages, or that they had a feebler activity, and the substances either split off too little iodine, or split it off with greater difficulty.

The relation of iodine content to thyroid activity has been known since Baumann<sup>48</sup> published his observations on the iodine content of the gland. Up to the present time the nature of the iodine complex in the gland is not known. Hunt and Seidell<sup>49</sup> attempted to find thyrotropic iodine compounds, testing them physiologically by the aceto-nitrile test. The only iodine compound, except that obtained from thyroid, shown to have any specific "thyroid" action was that from "bladderwrack," and that was much weaker in proportion to its iodine content than the thyroid

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44 Loeb, O. *Deutsch med Wchnschr*, 1911, **XXXVII**, 1006.

45 Erlenmeyer and Stein. *Therap Monatsh*, 1909, **XXII**, 133.

46 Winternitz. *Therap Monatsh*, 1909, Part 6.

47 Von Notthafft. *Monatsh f prakt Dermat*, Oct 15, 1910, abstr in *Jour Am Med Assn*, **lvi**, 685.

48 Baumann. *Ztschr f physiol Chem*, 1895, **XXI**, 319.

49 Hunt and Seidell. *Jour Pharm and Exper Therap*, 1910, **II**, 15.

substance itself. All other organic compounds studied were found to be relatively only about as active as potassium iodid, and they ascribe their action to their indirectly increasing the activity of the thyroid by increasing its iodin content. V Fuith and Schwartz<sup>50</sup> tested the action of iodized egg albumin when administered intravenously and found an action similar to that of iodothyron, i. e., it produced a fall in blood-pressure both before and after sectioning the vagi. No other thyroid activity, however, has been shown for it.

The giving of iodin in combination with other substances may sometimes lead to toxic action due to the rest of the molecule. This has already been pointed out for iodoform and its substitutes. Other substances, however, intended for use for their iodin content have shown a toxicity far greater than that of potassium iodid. Eeckhout<sup>51</sup> has shown iodival to have a hypnotic action, similar to that of bromural. Loeb and van der Velden<sup>52</sup> have shown that iodival is fatal to rabbits in doses of 0.5 gram per kilo weight. It is obvious, therefore, that such toxic compounds could not be used where the action of large amounts of iodin was desired. Boulaire<sup>53</sup> tested the comparative toxicity of various iodin compounds and found the iodized fats least toxic, both as to immediate and late effects, while he found iothion most toxic. (Iodival was not tested.)

#### V—CLINICAL REPORTS

As is to be expected, we have numerous reports of the use of various organic iodin preparations in practically every disease in which iodin or the iodids are recommended. Many writers have claimed that iodism is less frequent when an iodized fat, for example, is used in place of potassium iodid. We find, however, that in nearly every case these substances have been given in relatively small doses, and very few attempts have been made to increase the dose rapidly, as is often done with potassium iodid. One reason for this is undoubtedly the almost prohibitive cost of the organic preparations, when large amounts are desired.

Many observers have also shown that the stomach is less apt to be disturbed by the administration of organic compounds. This is to be expected when substances not acted on by the gastric contents are given, when the substances are not irritating themselves. In the case of commercial preparations containing free iodin we should not expect them to pass through the stomach without local effect.

Wintermiz,<sup>54</sup> O. Loeb<sup>55</sup> and Boruttan<sup>56</sup> agree that the organic iodin preparations are not to be regarded as substitutes for the alkaline iodids in every case, but that each class of compounds has its own special con-

<sup>50</sup> Von Fuith and Schwartz. *Pflüger's Arch.*, v, 125, p. 113.

<sup>51</sup> Eeckhout. *Arch. f. exper. Path. u. Therap.*, 1907, lxi, 338.

<sup>52</sup> Boulaire. *Compt. rend. Soc. de biol.*, 1906, lvi, 303.

<sup>53</sup> Boruttan. *Deutsch. med. Wchnschr.*, 1911, No. 43, p. 1975.

siderations which should be taken into account in the use of any of them Winternitz<sup>16</sup> recommends the use of iodipin in such cases as bronchial asthma, arteriosclerosis (luetic endarteritis) and lead-poisoning, on account of its slow splitting and prolonged excretion, and states that its use in special cases is well founded. The same considerations also apply to the other members of the iodized fat and fatty acid group, according to their relative rates of absorption, and excretion. We have less physiological grounds, however, for the giving of iodized proteins.

#### VI—CONCLUSIONS

From the evidence presented above as to chemical nature, absorption and excretion, distribution, physiologic action and clinical results, we may draw the following conclusions with regard to the therapeutic uses of the organic iodin compounds.

1 Up to the present it has not been shown that the organic iodin preparations, with the exception of preparations of thyroid, have any specific action in pathologic conditions, except the action of iodin after separation from the molecule.

2 The iodized proteins seem to be of advantage for therapeutic use only in so far as they avoid gastric irritation. The more stable compounds are apparently not entirely split in the body and are therefore not well utilized, while the less stable compounds have no advantages over the alkaline iodids, either as to local effects, or as to rapidity of absorption and excretion.

3 The iodized fats and fatty acids appear to have some advantage when the continuous action of small amounts of iodin is desired. They are more slowly and evenly split, and the amount of available iodin in the blood does not vary from time to time to the extent that it does when the alkaline iodids are administered. The use of the iodized fats in such conditions as arteriosclerosis, bronchial asthma, lead-poisoning, etc., probably has some rational basis, therefore, on physiologic grounds. These substances are also as a rule non-irritant to the stomach.

4 The difference in frequency of iodism is probably due to the difference in the amount of available iodin present in the body at any one time. When large amounts of iodin are desired, as in cerebrospinal syphilis, avoiding the danger of iodism would be at the sacrifice of therapeutic efficiency.

5 The use of organic iodid preparations with toxic side actions, due to the molecule or its splitting products, should of course be discouraged. The products of iodin with the higher fats and fatty acids are generally free from toxic actions.

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## THE GLYCYLTRYPTOPHAN (PEPTID) SPLITTING AGENT IN HUMAN SALIVA

FRANK SMITHIES, M D

ROCHESTER, MINN

Rather more than a year since, Warfield<sup>1</sup> claimed the discovery of a new enzyme in human saliva, "a substance which has the power to split glycyltryptophan" (a dipeptid). This hydrolyzing property of saliva was stated as being lost when saliva is acid or when heated to 100 C. Warfield's report bases his conclusions on the action on glycyltryptophan of twenty-eight specimens of saliva. Of this number, saliva was alkaline (where stated) in all the positive reactions and acid in all negative glycyltryptophan tests. The use of tobacco, observed in seven instances, did not materially alter the result so long as the salivas remained alkaline.

About six months after Warfield's communication, Weinstein,<sup>2</sup> in writing of the "tryptophan" test for carcinoma ventriculi, confirmed Warfield's findings. Weinstein's observations are indefinitely stated. The few experiments actually quoted admit of dubious conclusions (*vide* 1 to 3, and A-B). In a footnote Weinstein states that his colleague, Professor Gies, "although suggesting the probability of ereptic and tryptic excretion by the salivary glands, thinks it possible also that the tryptophan producing enzyme in mixed saliva is derived in part from the bacteria in the mouth, especially from cavities in carious teeth."

Previous to Warfield's report, ptyalin (diastase) had been considered the essential enzyme in human saliva. Maltase can hardly be regarded as distinctive. It would seem that if human saliva contain a proteolytic enzyme, new problems in the physiology of digestion would be presented.

The observations included in this report were made in the endeavor to determine the existence of the peptid-splitting agent in saliva, the nature of this agent and the conditions under which it might be evidenced.

\*Manuscript submitted for publication Sept. 9, 1912.

\*From the Division of Gastro-Enterology, Mayo Clinic.

1 Warfield. Bull. Johns Hopkins Hosp. May 1911.

2 Weinstein. Jour. Am. Med. Assn. 1911 Jan., 1920.

## AUTHOR'S STUDY

Three hundred thirty-four individuals furnished the specimens of saliva. They were of both sexes and ranged in age from 18 to 74 years. Three hundred eighteen specimens came from patients who presented themselves for test-meal examination of gastric function at St. Mary's Hospital (Mayo Clinic). Sixteen specimens came from laboratory assistants, nurses and physicians.

*Collection of Saliva*—In the test-meal cases, patients were fed the Ewald breakfast. From ten to twenty minutes after they had eaten they were furnished with large test tubes, into which they spat. They were instructed to furnish saliva and not nasopharyngeal accumulations or laryngo-bronchial sputum. The collecting test-tubes had previously been boiled in distilled water, hot and dried and plugged with sterile cotton. Saliva was collected for from forty-five minutes to one and one-half hours following the ingestion of the test meal. It was kept at room temperature in the test tubes, securely plugged, until the various experiments to be made with it were set up. Except in special instances (*vide infra*) experiments were set up within four hours following the collection of the specimens. The reaction of the saliva was always ascertained with wet litmus at the time the test mixtures were made. In each donor, the teeth, gums, and oral, nasal and pharyngeal mucosæ were inspected.

*Routine Procedure for Observation of the Peptid-Hydrolyzing Property of Saliva*—For testing the cleavage power of the specimens, the dipeptid-glycyltryptophan, was chosen. The preparation made under the direction of Neubauer and Fischer was used (Manufactured by Kalle & Co., Biebrich am Rhein, and secured through Noyes Bros. & Cutler, St. Paul, Minn.). This was obtained in small bottles and preserved under an ample layer of toluol. To guard against the crystallization out of the glycyltryptophan from solution, and the consequent doubtfulness of the results, the preparation was kept in a thermostat at 37° C.

The tests were, in general, set up as follows. Into each of a series of sterile test-tubes (those measuring 10 cm. by 14 mm. were found to answer very well) were poured, respectively, 0.3 cc. of the glycyltryptophan solution, 3 cc. of saliva and 0.5 cc. of toluol. Sterile pipets were used in measuring the quantities. In each series controls were set up consisting of (a) 0.3 cc. glycyltryptophan solution + 3 cc. sterile distilled water + 0.5 cc. toluol, and (b) 3 cc. saliva + 0.5 cc. toluol. The tubes were inverted several times to secure complete mixture of the ingredients. They were then placed in a thermostat at 37° C. for twenty-four hours. From each tube was next transferred to each of a set of small test tubes, 2 cc. of the mixture below the toluol layer. To each tube was then added 0.2 cc. of a 3 per cent glacial acetic acid in distilled water solution. The tubes were shaken vigorously. Test for free tryptophan was then made. Bromine vapor was allowed to flow into each test tube until the glass above its contents showed strong amber. The tubes were next shaken and note made of any color change occurring in the mixture. The presence of tryptophan was considered proven when the liquid took on lilac, rose pink, purple or magenta hues. The color changes were observed by daylight against a white background (filter paper). By this procedure, small amounts of free amino acid (tryptophan) are readily detected. Questionable reactions were usually due to the presence of very small amounts of tryptophan, dirty saliva, excess of bromine (as when bromine water is used instead of bromine vapor) or poor light.

1 *The Presence of Peptid-Splitting Agent in Whole Saliva*—In this series of tests a portion of saliva free from food particles, blood or nasopharyngeal mucus was examined first for free tryptophan. Reference to

Table 1 shows that of 334 specimens of saliva, but three showed free amino-acid before the dipeptid glycytryptophan had been added or the specimens had been incubated. All three positive tests were returned by dirty saliva from individuals with pyorrhea alveolaris and many decayed teeth. One individual had enlarged tonsils with ragged crypts filled with creamy exudate. Of the three positive tryptophan tests, two occurred in very acid saliva and one in neutral saliva (case with foul tonsils).

In this same series portions of the saliva (334 specimens) were incubated with glycytryptophan under toluol for twenty-four hours, as described above, and at the end of the incubation period were tested for free tryptophan. Table 1 shows the results.

It will be noted that irrespective of the reaction of the different specimens, 314, or 94.1 per cent, manifested some degree of hydrolytic power for glycytryptophan. Twenty, or 5.9 per cent, were negative, irrespective of reaction of the saliva. We shall comment on the significance of reaction below. It, however, seems proper here to call attention to the facts that of 334 specimens, 148 were neutral to wet litmus, and that of this number 139 (93.9 per cent) revealed free tryptophan after incubation. Acid reaction was shown by 163 specimens. Of these, 156 (95.7 per cent) were capable of splitting glycytryptophan. Of the twenty-three distinctly alkaline salivas, nineteen (82.6 per cent) showed free tryptophan after incubation with the test dipeptid. In view of the difficulty in accurately determining shades of difference in reaction between the neutral and alkaline salivas with litmus, we may fairly group the results from such specimens, in other words, of 171 specimens (neutral and alkaline) 154 (90.1 per cent) were able to hydrolyze glycytryptophan with resultant detectable amounts of free amino-acid.

Warfield's tabulation of twenty-eight specimens of saliva shows that in his series thirteen were from individuals affected with some form of gastro-intestinal anomaly while the remainder were from subjects in good health. In twenty-five specimens (89.3 per cent) he obtained cleavage of glycytryptophan (bromin water test). He states that all positive reactions were from individuals with alkaline salivas. We are unable to account altogether for the discrepancy between his figures and ours.

TABLE 1.—THE PEPTID SPLITTING POWER OF WHOLE SALIVA

No of Cases	Positive Reactions*			Neg Reactions	Tryptophan Test	Reaction of Saliva	Percentage
	+	++	+++				
148	23	61	52	0	1	Neutral	Pos 93.9 Neg 6.1
163	27	70	50	7	2	Acid	Pos 95.7 Neg 4.2
23	3	3	13	4	0	Alkaline	Pos 82.6 Neg 17.3+
334	53	146	115	20	3		

\*Degree of reaction: Lilac = +, rose pink = ++, rose purple = +++.

Total Pos. (all degrees) = 314 or 94 per cent.

Total Neg. (all degrees) = 20 or 5.9 per cent.



groups the preponderance of the reactions fall in grades ++ and +++ Twenty-six (75 per cent) of the salivas in our series came from individuals with artificial teeth Of this number 15 + per cent of the salivas did not split glycyltryptophan These were from clean mouths in three instances and from a dirty mouth in a fourth In this group (artificial teeth), thirteen (50 per cent) of the salivas showed very strong cleavage power In the majority of these, both artificial teeth and patients' mouths were very dirty

TABLE 3—THE RELATION OF THE CONDITION OF THE TEETH TO PEPTID SPLITTING POWER OF SALIVA

No of Specimens	Teeth—State	Reaction *			
		0	+	++	+++
84	Good	10	35	27	12
50	Fair	6	13	17	14
88	Poor	0	18	28	42
86	Very poor	0	21	18	47
26	Artificial	4	4	5	13

\*Degree of reaction Lilac = +, rose-pink = ++, rose purple = +++

(b) *Gums* Of 334 individuals, 201 (60 + per cent) showed erosions at the teeth-gum margins, or definite pyorrhea alveolaris Of this number, the saliva was acid in 149 instances (74.1 per cent) These specimens split glycyltryptophan in 189 instances (94.3 per cent)

(c) *Tonsils and Nasopharynx* Salivas were collected from 192 persons in which these parts were inspected In fifty-three instances (27.5 per cent) there was evidence of tonsillar disease (enlargements, crypts, exudate, erosion) In thirty-eight instances (19.7 per cent) there were evidences of nasopharyngeal inflammation In six instances (3.1 per cent) there were ulcerative conditions of the oral mucosa, apart from adenoid hypertrophy or pyorrhea

Of the 192 individuals whose tonsils, oral mucosa, etc., were examined, seventy-three (38 + per cent) revealed some abnormality Of this number forty-two (57.5 per cent) had acid salivas and thirty-one (42.4 per cent) of these salivas split glycyltryptophan after incubation for twenty-four hours at 37 C

(d) *The Use of Tobacco* Of the 334 specimens of saliva examined 209 came from males In 140 instances data were obtained regarding the use of tobacco Seventy-eight smoked or chewed tobacco, or both Three of these also used snuff Saliva from these seventy-eight individuals split glycyltryptophan in sixty-nine instances (89.8 per cent), irrespective of its reaction to litmus Twenty-five donors chewed tobacco but did not smoke regularly Eleven of these had acid salivas Twenty-two 'chewers' donated salivas which split glycyltryptophan in fifteen instances (68.1 per cent)

(c) *The Effect of Mouth-Washes* A water solution of alphozone of 0.4 per cent strength was used vigorously as a mouth- and teeth-wash in fifty-two instances. The subjects were directed to hold the solution in their mouths for several minutes, to force it back and forth between their teeth and about the alveolar spaces, and to gargle a portion. The mouth was then rinsed with warm normal salt solution. Saliva was then collected for forty-five minutes. From the fifty-two donors saliva was alkaline or neutral in thirty-eight instances (73 per cent) and acid in fourteen instances (26.9 per cent). From this group of fifty-two specimens cleavage of glycyltryptophan occurred but seventeen times (32.7 per cent). With respect to degree of cleavage, the reaction was in no instance beyond ++.

The results obtained after the use of the strong alphozone solution as a mouth-wash led us to test the effects of it and like solutions on saliva directly, and to experiment with mouth and throat cultures of bacteria.

5 *Consideration of the Effect of Temperature on the Peptid-Splitting Power of Saliva—Boiling* A portion of saliva from each of 302 specimens combining all reactions was immersed in a plugged sterile test-tube in water and kept boiling for thirty minutes, glycyltryptophan solution was added after the saliva had been cooled, and the mixture was then placed under toluol in the thermostat for twenty-four hours. Test for tryptophan was then made in the usual manner. In none of the boiled specimens could free amino-acid be detected.

*Room Temperature* Portions of 160 specimens of saliva were mixed with glycyltryptophan and left under toluol for from twelve to 120 hours, at room temperature (about 75 to 80 F). Table 4 summarizes the result.

TABLE 4—THE CLEAVAGE POWER OF SALIVA AT ROOM TEMPERATURE

No. of Specimens	Reaction	+ Reaction (Cleavage) after Hours							No. of Specimens Showing No Cleavage
		12	24	36	48	72	96	120	
66	Acid	3	7	29	16	5	4	0	2
82	Neutral	6	30	26	7	9	0	0	4
12	Alkaline	2	8	0	1	0	0	0	1
<hr/>		<hr/>							<hr/>
160		11	45	55	24	14	4	0	7

Briefly, it is seen that irrespective of the reaction of saliva, cleavage of the dipeptid occurs in the majority of instances between twenty-four and thirty-six hours after admixture, that in a few instances cleavage may have taken place within twelve hours or may be delayed ninety-six hours or no free amino-acid may be detected at the end of 120 hours (seven instances), that neutral and alkaline salivas split glycyltryptophan somewhat more rapidly than do acid salivas at room temperature.

*Ice-Box Temperature* Thirty-five specimens of whole saliva of the several reactions were mixed with glycytryptophan under toluol and kept on ice. Portions tested within twenty-four to 522 hours showed in no instance hydrolyzation of the dipeptid. Of these thirty-five specimens, after being on ice over 522 hours, twenty-nine were placed in the thermostat at 37° C, and twenty-six showed free tryptophan after eighteen hours.

*Graded Temperatures* Specimens of saliva were variously heated in plugged sterile test-tubes, cooled in running water, combined with glycytryptophan solution and placed in a thermostat under toluol for twenty-four hours. This mixture, acidulated, was then tested for free amino-acid. Table 5 shows the results.

TABLE 5—THE INFLUENCE OF GRADED TEMPERATURES ON THE PEPTID SPLITTING POWER OF SALIVA

No of Specimens	Reaction of Saliva	Reactions at Temperature													
		20 C	30 C	40 C	45 C	50 C	55 C	60 C	65 C	70 C	75 C	80 C	90 C	100 C	
28	Acid	25	22	26	23	23	21	22	14	8	1	0	0	0	
34	Neutral	33	31	29	30	26	26	24	22	21	3	0	0	0	
9	Alkaline	9	9	8	7	6	7	5	5	5	0	0	0	0	
<hr/> 71		<hr/> 67	<hr/> 62	<hr/> 63	<hr/> 60	<hr/> 55	<hr/> 54	<hr/> 51	<hr/> 41	<hr/> 34	<hr/> 4	<hr/> 0	<hr/> 0	<hr/> 0	

It is seen that, irrespective of the reaction of the saliva, of seventy-one specimens examined, there is uniform cleavage up to 60° C. Between 60 and 75° C, there is rapid diminution in peptid-splitting power, varying with reaction somewhat (neutral saliva being most resistant to increased heat). We never had any specimen show cleavage of glycytryptophan after it had been heated above 75° C. The variations in splitting power of the specimens with different reactions would appear to be somewhat dependent on such reaction although there may be other factors (thick, clumpy, or dirty saliva).

6 *Effect of Chemical Solutions on the Peptid-Splitting Power of Saliva* In these experiments the following solutions were used:

- 1 Phenol (carbolic acid) in water, 2 per cent
- 2 Bichlorid of mercury in water, 1 per cent
- 3 Alphozone in water, 0.1 per cent, 0.2 per cent, 0.3 per cent, 0.4 per cent
- 4 Antiformin (commercial solution)
- 5 Absolute alcohol
- 6 Acetic acid, glacial
- 7 Chloroform
- 8 Ferric chlorid solution, 5 per cent

*Procedure*—After specimens of saliva had been tested for free amino-acid and found negative, equal portions were respectively combined with glycytryptophan solution plus 1 c c of the solution of the chemical com-

bination under consideration Controls of portions of saliva without glycytryptophan solution and also of the glycytryptophan solution itself were set up The tubes were then incubated under toluol for twenty-four hours, when they were made acid (if not already acid) with 3 per cent acetic acid solution and tested for free tryptophan in the usual manner Table 6 shows the experiments and results in detail

TABLE 6—THE INFLUENCE OF CHEMICAL ACTION ON PEPTID-SPLITTING POWER OF SALIVA

No of Series	No of Specimens	Combination Tested	No of Positives	No of Negatives	Controls					
					Glycytryp- tophan + Saliva		Glycytryp- tophan alone		Saliva alone	
					Pos	Neg	Pos	Neg	Pos	Neg.
1	25	2% phenol + saliva and glycytryptophan	0	25	23	2	0	25	0	25
2	25	1% mercuric chlorid + saliva + glycy- tryptophan	0	25	25	0	0	25	0	25
3	25	Antiformin + saliva + glycytryptophan	0	25	21	4	0	25	0	25
4	25	Glacial acetic acid + saliva + glycytryp- tophan	0	25	23	2	0	25	1	24
5	25	Chloroform + saliva + glycytryptophan	0	25	24	1	0	25	0	25
6	25	5% ferric chlorid + saliva + glycytryp- tophan	3	22	24	1	0	25	0	25
7	80	Absolute alcohol + saliva + glycytryp- tophan	0	80	74	6	0	80	0	80
8	50	0.1% alphozone + saliva + glycytryp- tophan	32	18	46	4	0	50	0	50
	50	0.2% alphozone + saliva + glycytryp- tophan	24	26	46	4	0	50	0	50
	50	0.3% alphozone + saliva + glycytryp- tophan	11	39	46	4	0	50	0	50
	50	0.4% alphozone + saliva + glycytryp- tophan	0	50	46	4	0	50	0	50

It will be observed that solutions of 2 per cent phenol, 1 per cent  $\text{HgCl}_2$ , antiformin, glacial acetic acid, chloroform and absolute alcohol and 0.4 per cent alphozone absolutely inhibit the peptid-splitting agent in human saliva. A 5 per cent solution of ferric chlorid prevented cleavage in 88 per cent of specimens.

Brief attention may be called to the action of the alphozone solutions. After we had conducted the experiments on salivas from individuals who had used alphozone solution as a mouth-wash, we carried out a few tests (not included in the series of Table 6) in which we used a 0.1 per cent solution of alphozone combined with saliva. We found that several of

the thick tenacious or dirty salivas retained good cleavage power for glycyltryptophan even after so powerful an organic peroxid as alphozone had been added. When the experiments for Table 6 were set up, various strengths of alphozone were added in the attempt to discover the limit at which cleavage of the dipeptid was possible with this admixture. It is seen by Table 6 that only solutions so powerful as 0.4 per cent alphozone uniformly inhibit the peptid-splitting power of whole saliva and that diminution in strength of solution results in proportionate increase in the number of salivas which retain that power.

With exception of the alphozone and chloroform additions to saliva-glycyltryptophan mixtures in our series there were always various grades of precipitation in the combinations when the numerous test solutions were added. It would seem that this fact might seriously interfere with the action of the peptid cleaving agent in saliva, if that agent be an enzyme. Precipitation may not, however, be the only factor. Chloroform and alphozone admixtures produce no marked precipitation in saliva-glycyltryptophan solutions. Chloroform absolutely inhibited cleavage in our experiments. Alphozone solutions only inhibited cleavage of the dipeptid above 0.3 per cent strength. In addition to the question of increase in alkalinity in alphozone-saliva mixtures, as the percentage of alphozone increases in such solutions one must also consider the importance of alphozone as a germicide. Inasmuch as in our experiments alphozone was the only chemical agent added to saliva, which did not cause precipitation of protein, and yet did not invariably inhibit cleavage, its results only can be used to indicate a line of demarcation respecting a factor, at least, in explanation of how saliva splits glycyltryptophan. It is well known that chemicals that precipitate protein in enzyme-containing solutions, also inhibit the ferment action of those solutions. Inhibition of the peptid-splitting agent in saliva by such chemical solutions as phenol, mercuric chlorid, antiformin, alcohol and the like, leaves us in doubt as to whether or not such agent was rendered inert by precipitation of an enzyme with protein in saliva or cleavage power was lost by bactericidal action of these strong germicides, or both. Ferric chlorid solutions which precipitate protein in saliva are not very strongly germicidal, apart from mechanical action. In 88 per cent of specimens cleavage of glycyltryptophan was inhibited by 5 per cent ferric chlorid solution.

### 7 *Effect of Bacteria on Cleavage of Glycyltryptophan*

1. *Saliva + Bacteria*—Cultures from twenty seven specimens of saliva were made in (a) bouillon, on (b) nutrient agar and on (c) blood serum agar. These were allowed to remain three days in the water bath at 37 C. In reaction the salivas from which cultures were made were alkaline, three, neutral, fifteen and acid 9.

Table 7 gives details regarding salivas, organisms returned by cultures, etc. At the end of the incubation period, experiments were set up as follows:

TABLE 7—EFFECT OF BACTERIA ON CLEAVAGE OF GLYCYLTRYPTOPHAN

Series No	Patient's Number	Reaction of Saliva	Teeth	Organisms in Cultures	Results				Remarks
					Series a Pos	Series a Neg	Series b Pos	Series b Neg	
1	47285	Alkaline	Good	Streptococci, staphylococci, diplococci, short bacilli	+	0	0	+	
2	67218	Alkaline	Good	Cocci, lance-shaped bacilli	0	+	0	+	Adenoids
3	67232	Alkaline	False	Cocci, diplococci, spirillæ	++	0	0	+	
4	66886	Neutral	False	Diplococci, streptococci, short rods	+	0	0	+	
5	9596	Neutral	Good	Cocci and short bacilli	Tr	0	0	+	Pyorrhea
6	67244	Neutral	Fair	Cocci, rods and spirillæ	Tr	0	0	+	
7	67292	Neutral	Good	Staphylococci and streptococci lance-shaped bacilli	+	0	0	+	Diseased tonsils
8	67285	Neutral	Poor	Cercomonas in fresh specimen, cocci, spirillæ and rods	++	0	0	+	Pyorrhea ++
9	67328	Neutral	Good	Diplobacilli, diplococci, staphylococci	0	+	0	+	Pyorrhea
10	67352	Neutral	Good	Streptococci and staphylococci, few bacilli	+	0	0	+	
11	67338	Neutral	Fair	Micrococcus, streptococci, staphylococci	+	0	0	+	Dirty teeth
12	67368	Neutral	Good	Cocci, lance-shaped bacilli	?	0	0	+	
13	67336	Neutral	Good	Short rods, cocci, spirillæ	+	0	0	+	Pyorrhea+
14	67342	Neutral	Fair	Cocci, diplobacilli, leptothrix	Tr	0	0	+	Large tonsils
15	67313	Neutral	Good	Micrococci, streptococci, staphylococci, short bacilli	+	0	0	+	
16	28954	Neutral	Poor	Spirillæ in fresh bacilli, diplococci, and streptococci	++	0	0	+	Many carious teeth
17	67404	Neutral	Fair	Bacilli and cocci	+	0	0	+	Several cavities, pyorrhea
18	67365	Neutral	Good	Staphylococci, diplobacilli	Tr	0	0	+	
19	67206	Acid*	Poor	Diplococcus, streptococci and staphylococci, bacilli	++	0	0	+	Cavities in teeth
20	67213	Acid	Good	Streptococci, staphylococci, lance shaped rods	Tr	0	0	+	
21	51204	Acid	Fair	Micrococci, streptococci, rods	+	0	0	+	
22	67295	Acid	Fair	Staphylococci, streptococci, diplobacilli	+	0	0	+	
23	57318	Acid	Poor	Streptococci, staphylococci, bacilli, spirillæ	++	0	0	+	Carious teeth
24	67332	Acid	Very Poor	Staphylococci, streptococci short bacilli, diplococci, leptothrix	+	0	0	+	Many stumps and teeth with cavities
25	67268	Acid	Good	Cocci diplobacilli	Tr	0	0	+	
26	67431	Acid	Good	Cocci diplobacilli	Tr	0	0	+	
27	67371	Acid	False	Cocci, short and long rods	0	+	0	+	

Portions of salivas collected during the three days that the cultures were growing and which had been shown to be capable of splitting glycytryptophan, were heated at 100 C in a water bath for one hour. The specimens were then cooled in running water and made neutral with N/10 sodium carbonate. Two series were then made from the specimen: (a) Saliva + glycytryptophan solution + emulsions of bacteria from each set of cultures from saliva; (b) Saliva + glycytryptophan + toluol (Controls). The sets were then thoroughly mixed and incubated forty hours at 37 C. Portions of mixtures were then acidulated and tested in the usual way for free tryptophan. Table 7 shows the results.

It is seen that twenty-three out of twenty-seven salivas which had been rendered incapable of splitting glycytryptophan by heating to 100 C are capable of showing some evidences of cleavage power after being mixed with bacteria grown from specimens of saliva. In none of the controls was cleavage power exhibited. In sixteen out of the twenty-seven sets, free tryptophan was readily recognized on the addition of bromin vapor. In seven instances there was but a trace of free tryptophan. In one instance the result was questionable. In three experiments (11.1 + per cent) no free tryptophan could be detected. The reaction of salivas from which cultures were made appeared to have no great bearing on the results. Very rich flora in such salivas appeared to determine largely the degree of reaction. Rich flora were frequently present from salivas whose donors had very poor teeth or marked pyorrhea, but this was not constant. Nasopharyngeal conditions appeared to have bearing on quantity and variety of bacteria present in salivas.

Except as in Table 7, we have made no attempt to determine the exact organisms appearing to have some influence on cleavage of glycytryptophan, apart from noting the groups returned by cultures from each of the twenty-seven specimens of saliva examined. It would seem from the considerations of these groups that symbiosis of the organisms appeared to be responsible for certain ereptic power on glycytryptophan.

*B. Direct Effect of Cultures of Bacteria from Saliva Upon Glycytryptophan*—Transplants from the cultures from the twenty-seven specimens of saliva mentioned above (A) were made on fifty-four tubes of nutrient agar. These were incubated at 37 C for forty-eight hours. Growths resulted in all instances, the organisms being streptococci, staphylococci, micrococci, bacilli of varying lengths, diplococci and a few leptothrix.

To one half (twenty-seven) of the tubes was then added 0.5 cc glycytryptophan solution in 5 cc warm normal salt solution. To the remaining tubes 5 cc normal saline solution alone were added. The tubes were incubated thirty-six hours. At the end of incubation, the fluid from each tube was drawn off and after acidulation each specimen was tested for free tryptophan by bromin vapor. Table 7 gives details regarding the organisms.

*Result*—In none of the fluids from culture tubes to which normal salt solution alone had been added was free tryptophan shown. Twenty-one (77.7 + per cent) of the twenty-seven fluids from cultures where the glycytryptophan-salt solution had been added showed free tryptophan. The color changes ranged from pale lilac to rich rose pink.

## SUMMARY

From the work outlined in this report the following seems apparent

1. Reaction appears to have little bearing on power of saliva to split glycyltryptophan

2. Free tryptophan is occasionally met with in salivas from dirty or infected oral cavities

3. Centrifugalization of saliva lessens its power to cleave glycyltryptophan. This is rather more marked in alkaline or neutral salivas

4. Conditions of health and state of oral cavities of donors seem to affect reaction of saliva, with some apparent influence on the peptid hydrolyzing power of such saliva

5. Power to hydrolyze glycyltryptophan is lost when saliva is heated above 75 C. The optimum temperature for cleavage is about 37 C. At ice-box temperature cleavage is not carried on, but specimens kept at such temperature for as long as 522 hours, may hydrolyze the dipeptid when incubated subsequently at 37 C. At room temperature, cleavage is delayed, but is nevertheless carried on, apparently irrespective of the reaction of saliva

6. The chewing of tobacco seems to lessen the power of certain salivas to hydrolyze glycyltryptophan. Smoking of tobacco appears to have little effect

7. The use of strong mouth-washes (e. g., an organic peroxid, as alphozone) results in marked diminution of peptid-splitting power of certain salivas

8. Strong chemical action on saliva, particularly when the addition of such chemicals causes precipitation of protein, inhibits its glycyltryptophan splitting power. Many such chemical solutions tested in this report were germicides

Non-protein precipitating germicides (as the organic peroxid group) inhibit the peptid-splitting power of saliva roughly in direct proportion to strength of such solutions

9. Cultures of bacteria grown from salivas, may, after salivas have lost their power to split glycyltryptophan (by heating to 100 C.) cause such salivas to split that dipeptid by admixture with salivas and subsequent incubation

10. Solutions of glycyltryptophan added directly to cultures of bacteria grown from saliva are readily split with liberation of free tryptophan

11. The indefinite nature of any enzyme renders its actual demonstration difficult. While the agent in saliva causing cleavage of the dipeptid glycyltryptophan has certain characteristics of an enzyme, it would seem that a not inconsiderable factor in such cleavage power is the action of normal or pathologic oral microorganisms, or products of their growth



# A CONTRIBUTION TO THE SYMPTOMATOLOGY OF THROMBOPHLEBITIS IN TYPHOID

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Everyone who sees any considerable number of typhoid fever cases year after year must have been struck with the fact that, while most of these run a fairly typical and uneventful course, there is a very considerable group of cases in which the latter part of the course, or the period of convalescence, is marked by a number of obscure and apparently unrelated symptoms and complications. If one takes the trouble to read over a large number of case histories and charts of typhoid this fact is brought out even more clearly and forcibly, for many of these incidents are so transient and apparently insignificant that they fail to make much impression and are readily forgotten.

These symptoms include various forms of irregular febrile movement, sudden pulmonary and pleural symptoms, sudden and unaccountable abdominal symptoms, repeated chills, without obvious cause, pain, discomfort and stiffness in the legs or arms, pain in the heel, tenderness of the toes, etc. In some, but by no means in all, of these cases, frank signs of thrombophlebitis<sup>1</sup> appear at some time in the course of the illness.

It is my purpose in the present paper to attempt to show that many or most of these obscure late interruptions of the normal course of typhoid have a common underlying cause and that this cause is thrombophlebitis.

Before considering the individual symptoms it will be necessary to call attention to certain facts concerning phlebitis itself as it is seen in typhoid fever.

*Thrombophlebitis probably a much more frequent complication than is commonly supposed.* In most writings on the subject the incidence of this complication of typhoid is placed at about 2 per cent. In 829 cases studied by Osler<sup>2</sup> the percentage was 1.9. In Thayer's analysis<sup>3</sup> of 1,463

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1 In the present article the terms thrombosis and phlebitis are used interchangeably and without distinction to denote the whole process included in the longer term thrombophlebitis, and no attempt is made to settle the still uncertain and much discussed question as to whether the formation of the thrombus or the inflammation of the vein wall is the primary process. The weight of evidence at present, however, seems to favor the view that thrombosis occurs first.

2 Osler. *Studies in Typhoid Fever*. Johns Hopkins Hosp. Rep., III, p. 158 et seq.

cases venous thrombosis occurred in 26 per cent. My own belief is that these figures do not begin to represent the actual frequency of this complication. Among 1,540 cases of typhoid treated in the New York Hospital between 1898 and 1912 there were seventy-eight instances of undoubted venous thrombosis (5 per cent). If to this number be added the cases in which no thrombosis was recognized but which presented other symptoms that, as I hope to show, are usually indicative of the existence of a latent thrombosis, the percentage is increased to 8 or 9. Da Costa<sup>4</sup> reports that, in a series of 135 soldiers treated for typhoid in the Pennsylvania Hospital during the Spanish American war, the complication of milk-leg occurred sixteen times, or in nearly 12 per cent. Vincent,<sup>5</sup> in a group of cases studied by him, found the complication of phlebitis in 8.23 per cent.

It is my conviction that the further study of this complication in its various phases, and especially the more prompt recognition of its milder and less characteristic manifestations, will show that venous thrombosis occurs in from 10 to 15 per cent of all cases of typhoid fever.

*The development of thrombophlebitis is gradual, and its classical symptoms appear only late in the process.* The recent beautiful histological studies of Aschoff<sup>6</sup> show that the formation of the primary white thrombus is due to the gradual deposit, layer on layer, of blood platelets, while the blood is still flowing in the affected vein, in a manner somewhat comparable to the formation of a bar by the gradual deposit of silt in a flowing stream. The complete occlusion of the vein is a late phase of this process. The symptoms by which thrombophlebitis is ordinarily recognized—edema, pain, tenderness and periphlebitic induration—are seen usually only after such occlusion has occurred, for not until then do the signs of inflammation of the vein wall, and especially of the surrounding tissue, become pronounced. Up to that time the process of thrombosis either runs a latent course or manifests itself by symptoms so mild or so little characteristic that they are apt to be overlooked or misunderstood.

Vaquez,<sup>7</sup> in his admirable study of phlebitis, lays stress on the fact that this process need not result in complete occlusion of the lumen of the vein, and adds that "to wait until there is a total obliteration before saying that, clinically and anatomically, there is a phlegmasia alba dolens

3 Thayer. An Analysis of 42 Cases of Venous Thrombosis Occurring in the Course of Typhoid Fever. *Med News*, 1904, lxxxv, 637.

4 Da Costa. An Unusual Percentage of Cases of Milk Leg Following Typhoid Fever. *Internat Med Mag*, 1899, viii, 4.

5 Vincent. Bactériologie des phlébites dans la fièvre typhoïde. *Semaine méd*, 1895, xv, 377.

6 Aschoff et al. Beitrag zur Thrombosefrage. Leipzig, 1912.

7 Vaquez. De la phlébite. *Clin méd de la Charité*, 1894, p. 751.

is an error analagous to that made by waiting for the existence of pulmonary cavities in order to diagnosticate tuberculosis”

That extensive thrombosis of the veins of the extremities may develop without giving recognizable symptoms has often been demonstrated by the post mortem examination of patients dying of pulmonary embolism. The obstetrical, gynecological and surgical literatures abound with such instances. Vaquez,<sup>7</sup> in discussing the phlegmasia alba dolens which declares itself during the convalescence of typhoid, insists that the process itself often begins insidiously and latently long before the symptoms appear. In support of this statement it would be easy to cite many instances from among the typhoid cases included in this study, if space permitted.

*The thrombotic process in typhoid tends to be much more extensive and widely disseminated than the symptoms would seem to indicate.* One of the points brought out clearly in the present study is that the thrombosis is usually widely scattered and extensive even when the frank symptoms of the trouble may be quite circumscribed. For example, there may be slight pain, or muscular soreness, or points of tenderness in both calves and feet and then, some days or weeks later, distinct signs of phlebitis—i. e., marked tenderness and periphlebitic induration—only over a small area of one femoral vein. In other cases there will be frank signs of phlebitis only in one leg or thigh, and yet, some weeks later, after patient has been permitted to get up there will be marked edema of both legs. Not so very infrequently, in addition to phlebitis of the leg veins, there will be pain and more or less tenderness of one or the other arm. In one woman there was, in addition to phlebitis in both legs, distinct involvement of the veins of first one and then the other breast. Occasionally the process will seem to be confined chiefly to the small, superficial veins and will show a tendency to migrate from spot to spot over the legs, buttocks and lower part of the trunk.

#### THE PULMONARY COMPLICATIONS OF THROMBOPHLEBITIS

Although it is well known that pulmonary embolism is an occasional complication of venous thrombosis, attention has been centered chiefly on the large, fatal emboli which, while fortunately rare, are yet so dramatic in their occurrence and so tragic in their results as to leave a deep impression when they do occur. Such emboli usually result from the separation of a fragment from a thrombus occupying, and occluding, some large vein such as the femoral or iliac. They therefore are apt to occur late in the course of the phlebitic process. But there is another and much commoner type of pulmonary embolism which differs radically from that just

referred to in its time of occurrence, clinical course and prognosis, and which has received far less attention than it deserves

As a result of some personal experiences with this latter type I published recently a short paper<sup>8</sup> calling attention to the comparatively frequent appearance of small pulmonary emboli in the course of venous thrombosis and especially to the fact that such emboli in many cases make their appearance a number of days, or even two or three weeks, before any signs of thrombophlebitis can be detected. In seven of the nine cases reported the thrombosis had occurred in the course of typhoid fever. It seemed to me, therefore, that it might be instructive to go over the records of a large number of cases of typhoid with a view to ascertaining, first, what proportion of these cases complicated by phlebitis showed evidences of such pulmonary embolism, and, second, what proportion of the pulmonary and pleural complications of typhoid could reasonably be ascribed to pulmonary embolism and infarction. With these points in mind the records of all cases of typhoid treated in the New York Hospital between 1898 and 1912 in which the complications of phlebitis, pneumonia or pleurisy were recognized have been carefully analysed, and the results of this analysis form the basis of this paper.

Among the 1,540 cases of typhoid there were eighty-eight with pulmonary or pleural complications, exclusive of bronchitis. Among the eighty-eight cases there were twenty-five (28 per cent) in which the thoracic complications were almost certainly *not* of embolic nature. (These twenty-five cases formed a group having a strikingly uniform and sharply defined clinical picture. Almost without exception the pulmonary symptoms appeared early in the disease and began as a severe general bronchitis. This grew progressively worse and sooner or later resulted in bronchopneumonia, which was usually double and which usually involved the greater part of both lower lobes. Seventeen of these cases terminated fatally.)

There were eight cases (9 per cent) complicated by phlebitis which showed, at some time, pulmonary symptoms, but these symptoms were either not sufficiently characteristic or the records not sufficiently complete to warrant their being included among the cases of pulmonary embolism. Some of these cases, however, were almost certainly of this nature.

There were, further, twenty-six cases (30 per cent) in which the character of the thoracic symptoms made it seem very probable indeed that they were instances of pulmonary embolism but in which the records furnished no other evidence of thrombophlebitis. Finally there were twenty-nine cases (33 per cent) in which there were frank signs of

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<sup>8</sup> S. Conner, L. A. Pulmonary Symptoms as Premonitory Signs of Venous Thrombosis. Med. Rec. New York, April 29, 1911.

phlebitis and in which the pulmonary or pleural symptoms could be assumed with reasonable certainty to be due to embolism and infarction

Among these twenty-nine cases of pulmonary embolism nineteen gave their symptoms of this condition before the phlebitis had declared itself and ten after the signs of phlebitis had appeared

The above figures may be tabulated thus

	Cases	Per cent
Pulmonary and pleural complications (exclusive of bronchitis)	88	
Pulmonary embolism before appearance of phlebitis 19	} 29	33
Pulmonary embolism after appearance of phlebitis 10		
Phlebitis with pulmonary symptoms of doubtful nature	8	9
Probable pulmonary embolism without evident phlebitis	26	30
Pulmonary complications not embolic	25	28

The evidence on which is based the conclusion that a very large proportion of the pulmonary and pleural complications of typhoid are embolic in nature is and necessarily must be chiefly circumstantial. Such emboli are almost always small, the patients rarely die, and none of our cases has come to autopsy. Since the evidence is largely circumstantial its force depends on the accumulation and massing of it. It has therefore seemed to me necessary to record, in condensed form, all of the case histories. Whoever has the patience to read through these, case after case, will be likely to recognize a fairly distinct clinical picture, and in reading the cases of probable embolism without evident phlebitis will be convinced, I believe, that most of them are really cases of embolism.

The character of the records of the medical service of the New York Hospital probably does not differ materially from that of records of other hospitals of the same class. They have the failings inherent in a system which places chiefly on the, often overworked, intern staff the responsibility for the proper recording of the progress of the patients and of most of the daily events of the wards. These failings are usually chiefly sins of omission. Many transient and apparently unimportant symptoms, which may have been promptly recognized and properly cared for, are yet not noted in the permanent records of the patient. It is reasonable to assume, therefore, that the records of the cases under consideration sometimes fail to include facts that might have served to identify a mild phlebitis or a small pulmonary embolism and that the figures as given above if they err at all, do so on the side of conservatism.

#### SYMPTOMS OF PULMONARY EMBOLISM AS SEEN IN TYPHOID FEVER

As has been said already there are two quite distinct types of pulmonary embolism. In one the embolus is large, the attack is violent and usually fatal, and the symptoms, as a rule, appear only late in the course of the phlebitis. In the other the embolus is small the symptoms are often very mild and transient, the prognosis is good and the attack, in a majority of the cases, occurs some days before any of the usual symp-

toms of phlebitis can be discovered. The first type is rare, the second is relatively common. In the latter type the character of the symptoms and the time of their occurrence make it highly probable that these small emboli are derived from the freshly forming and friable mural thrombus before it has occluded the vein and while the blood is still flowing past it. That is the time when the thrombosis usually gives no local symptoms and the time also when one would naturally expect small particles to be carried away into the venous blood stream. Indeed, it is difficult to conceive of the gradual formation of a thrombus, by the deposit of blood platelets on the wall of a still patent vein, without some fragments being washed away and ultimately deposited in the lung capillaries, and one is inclined to wonder, not at the frequency of embolism in the early stages of thrombosis, but rather that a case of thrombosis should ever run its course without such early pulmonary emboli.

The observation that phlebitis may give rise to pulmonary embolism long before it manifests itself by local symptoms is by no means a new one. Vaquez,<sup>9</sup> in describing various modes of onset of phlebitis, speaks of one under the caption "Phlébite latente à début embolique." Such patients, in the course of some affection likely to be associated with phlebitis, "suddenly feel a stitch in the side followed by a little fever, sometimes with some bloody sputa. The trouble, which may be ascribed to an intercostal neuralgia or to a slight focus of congestion, rapidly disappears, then sometimes the same phenomena are repeated two or three times. Finally eight, ten or fifteen days afterward a phlebitis suddenly appears in one of the extremities."

Vialard<sup>9</sup> reports four examples of early pulmonary infarction in phlegmasia alba dolens. A number of such instances can be found also among the cases reported by Mahler<sup>10</sup> and by Zurhelle.<sup>11</sup>

A study of the cases cited by Osler<sup>2</sup> in his exhaustive "Studies in Typhoid Fever" shows this same association of obscure pulmonary and pleural symptoms with phlebitis. For example, Case 13,813 is cited among the cases complicated by pneumonia and also among those complicated by phlebitis. Cases 17,319 and 18,156 are mentioned under the heading of the complication of pleurisy and under that of phlebitis. Case 13,524 appears under the three groupings of "painful legs," pleurisy, and post-typhoid elevation of temperature.

An analysis of the twenty-nine cases of pulmonary embolism occurring with known phlebitis shows that *thoracic pain* was present at some

<sup>9</sup> Vialard. Des embolies pulmonaires préphlébitiques pendant les suites de couches. Jour de méd et de chir. 1904, lxxv, 62.

<sup>10</sup> Mahler. Thrombose Lungenembolie und plotzlicher Tod. Arbeit a d koenigl Frauenklinik in Dresden 1895, 11, 72.

<sup>11</sup> Zurhelle. Thrombose und Embolie nach gynäkologischen Operationen. Arch f gynäk, 1907, lxxiv 443.

time in almost every case. In a majority of the cases it was the first symptom noticed. The pain was usually sudden, sharp and severe and was felt commonly in the lower part of one or the other axilla. Occasionally it was referred to the hypogastrium, the shoulder or the lower part of the neck. The duration of the pain varied from a few hours to a number of days. *Cough* was present in most but not in all cases. In eight instances it was the first symptom. Sometimes it did not appear until two or three days after the onset of the pain.

*Bloody sputum* was noted in thirteen (45 per cent) of the cases. It sometimes appeared promptly, but frequently was seen only several days after the onset of the attack. Often the blood-spitting continued for many days. The blood was raised usually in small clots or streaks. At the onset such sputa are usually bright red, they soon become dark, however, and, if the spitting continues for many days, the altered blood gives a brownish color to the sputum. True rusty sputum was never seen.

*Sudden thoracic oppression and dyspnea* were present at the onset of the attack in only three cases. In five instances the pulmonary attack was introduced by one or more *chills*.

The behavior of the *temperature* varied much. In some cases it rose abruptly with the advent of the thoracic symptoms, but often it was not easy to determine whether the variations in the temperature were to be ascribed to the phlebitis, to the embolism or to the primary disease.

Rigidity of the upper portion of the abdominal musculature, and tenderness just below the ribs were present in several cases in which the infarction seemed to be situated at the diaphragmatic surface of the lung.

*Multiple Embolism*. In thirteen of the twenty-nine cases the symptoms were such as to indicate the occurrence of two or more attacks of pulmonary embolism. Among the cases of probable embolism without signs of phlebitis there were five in which the multiple character of the pulmonary attacks leaves little room for doubt as to their true nature. In one of these (Case 39) there were four distinct attacks during a period of three and a half weeks.

*Fatal Embolism*. Death occurred in three of the twenty-nine cases of pulmonary embolism with recognizable phlebitis (Cases 22, 27, 28). In each instance the fatal attack occurred late in the course of the phlebitis and had been preceded by milder pulmonary attacks.

*Physical Signs*. As regards their physical signs the cases may be divided into three groups:

1. Those in which friction rubs or crepitant râles over a small area were the only signs. These signs often lasted only two or three days.

2. Cases in which the signs were those of a small, circumscribed pneumonia. The area of consolidation did not extend and in each

instance the signs of consolidation disappeared within three or four days. These signs were almost always in the lower lobes.

3 Cases with signs of extensive plastic pleurisy or of pleural effusion. This type included more than half of all the cases. In some of these the physical signs at first were those of consolidation. It seemed to be quite characteristic of the third group of cases that although the signs seemed to indicate the presence of liquid, exploratory puncture usually failed to reveal it. In only three cases was serum obtained and in only one of these was there any considerable quantity.

#### CASE REPORTS

##### PULMONARY EMBOLISM BEFORE THE APPEARANCE OF SIGNS OF THROMBOPHLEBITIS

CASE 1—D R D, male, aged 32. No 1373. Admitted October 23, 1898, on ninth (?) day of illness. On this day patient developed a troublesome cough. On the next day (October 24) the sputum was blood-streaked. October 26, "Patient raised quite a considerable amount of blood." The cough and bloody sputum lasted for several days. On November 6, there was pain in the left groin and leg and two days later "tenderness in calf and along course of the long saphenous vein." Later still the leg became edematous. The temperature, which had been normal, rose for two days with the appearance of the signs of phlebitis.

CASE 2—W B, male, aged 26. No 2806. Admitted Aug 31, 1899, on ninth day of disease. Five days later (September 4) patient had a chill at noon and three hours later became very cyanotic, vomited, had a rapid, weak pulse and began to cough up blood-streaked mucus. September 12, had chill and became cyanotic. September 13, two chills. Over lower part of right chest behind, dullness, bronchovesicular breathing and crepitant râles. September 14, "Patient cyanotic, pulse very weak." During the next three days several chills. September 19, pain in right leg. September 20, signs of fluid over lower part of right chest behind. Pain, tenderness and swelling appeared in right thigh and calf. On September 27, pus was evacuated from right thigh, and on October 12, pus was discovered in right calf. Later there developed pain, tenderness and redness along the lower part of the inner side of the leg which persisted for a fortnight or more and gradually disappeared. The chest signs slowly disappeared and the patient recovered.

CASE 3—M B W, female, aged 24. No 2987. Admitted Oct 12, 1899, on fifth (?) day of illness. Severe course with persistent nausea and vomiting. October 17, patient had a chill with sweating, and soon afterward began to have severe abdominal pain. On the following day the pain was very severe and was localized over the right side of the chest. October 23, pain appeared in left leg and popliteal space. October 27, pain in left side of chest. October 29, pain began in right leg. November 2 and 4, chills. Pain in legs continued and on November 11 there was tenderness along the course of the femoral vein in both thighs. On the evening of November 17 there was a chill followed by sudden, severe pain referred to the region of the right shoulder and the patient was delirious through the night. All the symptoms gradually subsided and the patient recovered.

CASE 4—D P T, male, aged 24. No 6593. Admitted Nov 23, 1901, on twenty-first day of illness. The patient was delirious and very sick. Over the left lower lobe there was an admission dullness, diminished breathing and subcrepitant râles. On November 28 there was bronchial voice and breathing at the level of the angle of the scapula and signs of fluid below this. November 29, "area of consolidation unchanged. Signs of fluid much less." December 3, "Pain and tenderness along course of both internal plantar nerves." This pain in soles of feet



was troublesome for some days. On the night of December 16, patient developed a troublesome cough and on following day began to have very severe pain in right side of chest and in right shoulder, and the temperature rose from 100 to 104 F. The pain and cough continued through the night and next day over the right lower lobe there were signs of fluid and that evening twenty-five ounces of clear fluid were removed. December 23, "Patient complaining of pain in right leg and groin for several days. Tenderness is very marked over veins of thigh, where a cord can be felt." The phlebitis ultimately subsided without edema.

CASE 5—M M, male, aged 18. No 8179. Admitted Sept 21, 1902, on fifth day of illness. Ran a fairly severe course. No pulmonary signs or symptoms on admission. September 27, at 5 p m, the patient began to have very severe pain over left lower chest and in epigastric region, and temperature rose to 105.8. Patient was delirious much of the time for several days. No definite signs in the chest. October 11, "Has improved very much. Mind quite clear. Complaints of pains in left thigh and there is slight tenderness along course of the femoral vessels. For several days patient has been complaining of painful feet and his toes are very tender." October 13, "Complaints of left arm being painful and is unable to bend elbow." November 15. Tenderness along course of femoral vein had disappeared, but toes still somewhat tender. Good recovery.

CASE 6—W C G, male, aged 40. No 8467. Admitted Nov 17, 1902, on ninth day of illness. Very severe course, delirious much of time. November 21. Sudden pain in left chest, followed by coughing. November 22, 3 a m. Sudden cyanosis and dyspnea. Dyspnea continued throughout day. Troublesome cough. During next three weeks much coughing and frequent sweats. Beginning December 12, frequent chills and sweats. December 15. Severe pain in right leg followed by signs of phlebitis in thigh and leg. December 20. Pain in right chest and great restlessness. More cough. December 26. Signs of phlebitis in left calf. Return of pain in right chest. January 4. Small area of dulness and a few crepitant râles in (right?) lung. Sputum streaked with blood. January 5. Patient developed signs of edema of the larynx and died in spite of a tracheotomy.

CASE 7—J D, male, aged 12. No 9879. Admitted Sept 6, 1903, on fourth day of illness. Ran severe course. September 13 and 14, intestinal hemorrhage. September 21. Area of dulness near angle of right scapula with bronchial breathing and voice and many coarse râles. The cough and signs of consolidation lasted several days. September 27. Complained of pain in left leg, most marked along inner side of thigh where there is tenderness but no cord to be felt. Next day the temperature rose and continued high for some days. October 1. "Consolidation clearing up. Toes of both feet are tender." October 5. Toes no longer tender, and tenderness along inner side of thigh has disappeared. No further symptoms.

CASE 8—R A R, male, aged 27. No 10,130. Admitted Nov 14, 1903, on tenth day of disease. Ran a moderately severe course. Lungs normal on admission. November 16. Right wrist painful and tender. November 21. During the night there was sudden severe pain in right side, requiring anodynes. The pain continued through the day, without other physical signs. November 25. "Abundant fine pleuritic râles in right axilla and at right base." The pains and the signs of plastic pleurisy continued for several days. The pain tenderness and redness of right wrist also continued and extended to the palm of the hand. December 5. "Right wrist and hand not swollen but still somewhat tender. Today there is pain and tenderness in the left popliteal space and the left calf is somewhat swollen." Later the thigh became swollen and tender along the course of the femoral vein and a tender cord could be felt in the popliteal space.

CASE 9—J M, male, aged 18. No 14,283. Admitted to hospital Aug 31, 1906, on fifteenth day of illness. Severe course. Slight cough on admission. "Lungs normal except for a few scattered râles." September 2. Chill at 4 p m with rise of temperature to 105.6 F. at 8 p m, a second chill, temperature 106.6 F. respiration 36, pulse 124. September 3. Chill at 8 a m and again at 7 p m.

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No cough, pain or expectoration noted September 5 Chill September 6 Pain referred to left shoulder Slight resistance and tenderness in left upper quadrant of abdomen Chill at 11 p m September 7 Chill at 7 30 a m Severe pain in left chest, relieved somewhat by strapping chest September 8 "Patient has had three attacks of severe pain in left side, each time accompanied by profuse sweating Many fine crepitations over left lower back and in left axilla, brought out after coughing" September 11 Pain gone Signs of fluid over lower half of left chest, but needle inserted in two places revealed no fluid September 12 Chill at 6 p m temperature 106.4 F, respiration 40, pulse 140 September 14 Chill at 6 p m September 17 Temperature normal "At left base, dullness, diminished fremitus, a few rales and soft bronchial breathing" On September 18, 19 and 20 some elevation of temperature without apparent cause September 23 Temperature up Pain in left groin and tenderness from groin down inner side of thigh to popliteal space September 24 Cough more troublesome "Is raising bloody sputum today" Some dullness with diminished breathing and voice at right base The signs of phlebitis in the left thigh and leg lasted for some time The leg became edematous and some weakness and foot drop were noticed when the patient attempted to walk The patient made a slow but complete recovery

CASE 10—J M, male, aged 28 No 14,943 Admitted Feb 18, 1907, on the fourteenth day of illness Patient had a dry cough on admission and on evening of the same day spat up considerable bloody sputum February 22 "Marked dullness over entire right lower lobe, diminished breathing and many crepitant and subcrepitant rales" Cough and bloody sputum continued for some days February 25 Pulmonary signs unchanged Sputum had become foul smelling and dark in color A needle inserted in lower part of right chest behind withdrew thick, dirty red, foul-smelling material The signs of a gangrenous abscess in the lung gradually subsided and the temperature fell to normal On March 15 patient sat up for first time March 20 Marked signs of phlebitis in both legs, severe pain tenderness and edema Gradual recovery

CASE 11—S B, male, aged 34 No 15,227 Admitted April 14, 1907, on twenty-first (?) day of disease On April 16 and 17 there are notes of abdominal pain and rigidity, but the position of the signs is not given April 21 "Pain in the right side on breathing or coughing A few friction sounds in right axilla Below angle of right scapula there is dullness and diminished breathing" April 24 Right chest aspirated 175 cc of clear fluid obtained April 27 "Sputum brownish-red" April 30 "Sputum still bloody and foul smelling" On May 8, a needle inserted into right chest, posteriorly, revealed pus and patient was transferred to the surgical service and operated on for a pulmonary abscess Patient was allowed up on June 9, and two days later there were signs of phlebitis in both legs, with marked edema Slow recovery

CASE 12—J S female aged 35 No 15,687 Admitted to hospital July 3, 1907, on thirteenth day of illness Ran a moderately severe course, the fever gradually falling so that on the twenty-second day (August 8) the temperature remained below 100 F On August 9, at 8 a m, patient had a normal temperature and felt well At 8 40 a m she complained of acute pain in the region of the heart became cold and blue and broke out in a cold sweat She complained of three such severe attacks of pain within an hour The pulse rose from 76 to 116 the respirations from 20 to 44, and the temperature from normal to 103.1 During the afternoon and evening there were frequent paroxysms of pain in the chest the patient was cyanosed and cold, the pulse rapid and feeble There was also rigidity of the upper part of the left rectus muscle with tenderness August 10 and 11 there was troublesome dry cough with more or less pain in left chest Pleuritic friction sounds could be heard in the left axilla and was a distinct pleuropericardial rub August 12 "Patient still so cyanotic Dry cough and pain in left axilla still persists" August 13 accompanied by blood stained expectoration Impaired resonance, feeble

and many crepitant râles at right base posteriorly, and many crepitant râles in left axilla. August 14 "Sharp pain in right side of neck and right shoulder. Troublesome cough but no expectoration." August 17 Dull ache in left thigh and groin which next day extended to left calf. August 19 Sudden stabbing pain in right chest. August 20 Expectoration of bright blood which continued for several days. On August 26 there developed pain, tenderness and swelling along the course of the right femoral vein, the tenderness extended up along the course of the external iliac vein, and there was swelling and tenderness of the labium majoris on that side. August 30 Pain referred chiefly to sole of right foot. Later edema appeared in both legs. The chest signs gradually cleared up and patient made a good recovery.

CASE 13—Mr H, aged 50, was admitted Sept 2, 1910, on second day of illness. Course mild and uneventful until September 19. He then developed a troublesome cough to which was added, on September 22, pain in left side of chest which, for a day or two, was very severe. On the night of October 6, he had a chill and, a few hours later, severe pain in the left scapular region and cough. The pain and cough lasted for some days. On October 10 he spat up some bright blood streaked mucus and for several days afterward the sputum contained dark blood. On October 15 he began to have pain and tenderness in right leg which, two days later, extended to the thigh along the course of the femoral vessels. On October 26 the same symptoms appeared in the left leg and about the same time he suffered greatly for several days with pain in the lumbar portion of back. The phlebitis in both legs ran a long and severe course. The temperature, which had reached normal, rose abruptly on October 7 after a chill and continued high and irregular throughout the course of the phlebitis.

CASE 14—L C, male, aged 29. No 20,379. Admitted Sept 9, 1910, on sixth day of disease. Mild course, uneventful until September 21, then sudden severe pain referred to right hypochondrium, rapid breathing and rigidity of upper part of right rectus muscle. That evening, "many crackling pleuritic râles in right axilla." One week later, "slight tenderness along inner side of right leg." No further notes on the condition of the legs. Discharged October 22. A few days later friends of the patient reported that he had "swelling of both legs below the knees."

CASE 15—F Z, male, aged 32. No 20,513. Admitted Oct 3, 1910, on ninth day of disease. Uneventful and rather mild course until October 22, when he complained of pain in left axilla and had "a few fine pleuritic râles" in the same region. On the next day the entire left leg seemed slightly swollen, was bluish in color and there was marked tenderness over the femoral vein. October 24, "marked tenderness in abdomen just above left Poupart's ligament." October 29 Tenderness in right thigh. November 1 "Pleural friction rub low in left axilla." When discharged there was still some edema of left leg.

CASE 16—H C, male, aged 21. No 20,632. Admitted Oct 25, 1910, on the eighth day of disease. Ran a moderately severe course. November 6. In afternoon the patient began to cough severely and continued to do so for a number of days. November 13. Complained of pain in side of chest on breathing. "Low in left axilla and posteriorly over left lower lobe are scattered coarse friction rubs." November 22 to 26. Intestinal hemorrhages. The temperature, after having been normal for two weeks, rose abruptly on December 7 and continued fairly high for a fortnight or more. On December 11 signs of phlebitis appeared in the right thigh and later showed also in the right calf. There was no edema.

CASE 17—Mrs L, aged 43. Admitted Dec 18, 1910, on about the tenth day of disease. Moderate initial course followed by equally long "relapse." For about one week, beginning December 24, patient coughed much and had bloody expectoration. Later a few fine râles could be heard in both axillae and in both bases behind. January 22 patient began to complain of pain in left arm. On January 27, pain began in right leg and a few days later in the left leg. The pain was

especially severe and protracted in the left leg where there was marked tenderness over the lower third of the anterior surface external to the tibia. At the time of discharge there was still slight edema of the foot and ankle.

CASE 18—A C, female, aged 37. No 180,098. Admitted Nov 24, 1911, on eighth day of illness. Moderate course. Temperature gradually falling and patient conscious and comfortable when at 9 p. m. on December 4 (eighteenth day) she complained of sharp pain in left side of chest. The pain continued next day but the signs in the chest were negative except for many fine râles at the end of inspiration. Patient spat up a small amount of bright blood. December 7, "Still spitting up a small amount of bright blood occasionally. Still no definite signs in chest." No pain or tenderness along course of veins of legs. December 8. Still coughing. In a. m. complained of pain in right heel. Later in the day there was slight pain in right knee. "Still no signs of phlebitis." The temperature, which had been below 100° F. for some days, rose in the afternoon to 104° F. and remained high for four days. December 9. Slight tenderness over position of Hunter's canal and in popliteal space of right leg. December 12. Patient complained of more pain in left side of chest. December 13. Cough much worse. Sputum again contained bright blood. Pain in left knee. "No signs of phlebitis on that side." December 14. Tenderness over Hunter's canal on left side. December 15. Severe pain in left side of chest. At left base, dulness and many fine râles. The cough and bloody sputum continued for several days longer. The phlebitis of both legs lasted for some time and subsided without edema.

CASE 19—H P, physician, aged 24. Onset June 9, 1910. Moderately severe course which was uneventful until the evening of twelfth day (June 21) when he was awakened by sudden, severe, thoracic oppression and a feeling of suffocation. He had dyspnea, cyanosis, cold sweat, a rapid, thready pulse and all the indications of alarming collapse. On the following day these symptoms had somewhat subsided. Examination of the chest was negative. June 23. Symptoms subsiding. Lungs negative except for diminished breathing and crepitant râles at angle of left scapula. In the afternoon began to have pain in left side of chest which on following day (June 24) became very serious. Very slight cough. No signs of phlebitis. June 26. Began to expectorate mucus mixed with dark blood. June 28. Sharp pain in right side of chest. June 29. Soreness in calf of right leg which, on following day, extended along the course of the femoral vein in thigh. The bloody sputum and cough continued for some days longer. July 5. Some pain in left calf. No further symptoms until July 14 when signs of phlebitis in left femoral vein appeared. The signs of plastic pleurisy in the left chest slowly disappeared and patient made a good recovery.

#### PULMONARY EMBOLISM AFTER THE APPEARANCE OF SIGNS OF PHLEBITIS

CASE 20—W E S, male, aged 25. No 1572. Admitted Dec 4, 1898. Typhoid began in Porto Rico on October 8. Improved until November 13, when right leg became tender and swollen. This improved and patient left hospital. Two days before entrance to New York Hospital (December 2) the left leg became swollen and tender in the calf and on the following day, he had pain in left chest near his heart. On admission there was dulness and diminution of voice, breathing and fremitus at the left base and signs of phlebitis in the left leg. Recovery.

CASE 21—H W W, female, aged 25. No 2966. Admitted Oct 7, 1899, on tenth day of illness. Severe course. October 14. Pain and tenderness along course of femoral vein in right thigh. Chills October 17 and 18. October 22. Very severe pain in left side which was followed by signs of pleurisy with effusion in left chest. October 23. Signs of phlebitis in left leg. Later edema of both legs.

CASE 22—J L L, male, aged 26. No 6393. Admitted Oct 14, 1901, on sixteenth day of illness. On day before admission began to have severe pain in left thigh and leg and on admission showed well marked signs of femoral phlebitis. October 21. Soreness and tenderness in left heel, which lasted several days. October 23. Sudden change for the worse with very rapid pulse and breathing

October 24 Pain in right side of chest, with many friction sounds October 27, Chill, with rise of temperature and labored breathing Over lower part of right chest, flatness and diminished breathing, voice and fremitus October 30 Small amount of fluid obtained from right chest October 31 Signs of phlebitis in right leg Very severe pain and tenderness in foot and heel which lasted some days November 17 Sudden death, due probably to pulmonary embolism No autopsy

CASE 23—S H C, male, aged 32 No 9892 Admitted Sept 8, 1903, on fourth day of illness Very severe course September 14 Pain in left popliteal space September 18 Chill September 23 Slight edema of left ankle Tenderness and swelling of right calf September 25 Severe chill September 27 Chill Dulness and many crepitant rales at left base posteriorly September 28 Coughing Two chills Signs of consolidation at left base more distinct October 9, Still signs of phlebitis in both legs October 11 Two profuse sweats October 12 Chills Slight dulness and many crepitant rales over upper part of left lower lobe Signs of fluid at base Small amount of bloody fluid aspirated

CASE 24—Miss H P, aged 25 No 13,748 Admitted April 6, 1906, on seventh day of illness Long, severe course April 21 Began to complain of painful and tender toes, also of pain in both legs, but especially in left leg April 23 Tenderness in right groin below Poupert's ligament April 25 Cough and expectoration with rales at base of right lower lobe Between April 26 and May 22 patient had eight severe chills with fever of markedly remittent type During most of this time she suffered greatly from tenderness and pain in the toes May 6 Frank signs of phlebitis in left leg and later in thigh May 22 After a chill patient had a violent attack of coughing and complained of severe pain in left chest For several days thereafter severe pain in left chest and left upper quadrant of abdomen Irregular temperature continued for a fortnight longer

CASE 25—V A, male, aged 42 Admitted Feb 8 1910, on sixth day of illness Long severe course February 19 Chill and later pain and tenderness over left femoral vein Up to that time he had had no cough whatever That night he was disturbed several times by coughing attacks which ceased next day February 26 Chill, high temperature and signs of phlebitis of right femoral vein March 5 Sudden, severe pain in right chest, cough, bloody sputum, dulness and rales at right base posteriorly Later signs of consolidation in right lower lobe became more distinct Cough and expectoration of blood lasted for two weeks Slight chills with rise of temperature on March 15 and 25 On March 15 patient complained of great tenderness in toes of both feet, which continued for several days Later edema of both legs No rise in leukocytes

CASE 26—M P, male, aged 23 No 20,248 Admitted Aug 22, 1910, on eleventh day of illness Moderate course and uneventful convalescence until September 20 Patient had been up and about ward for several days and on this day temperature began to rise On the following day there was pain in left thigh but no other indications of phlebitis Later in the day there developed pain in right side of chest, made worse by deep breathing, and a few friction rubs could be heard in the right axilla The pulmonary symptoms soon disappeared All the usual symptoms of femoral phlebitis developed rapidly and lasted for two weeks

CASE 27—D C male aged 23 No 178,211 Admitted July 20, 1911, on fourteenth day of illness He then complained of pain in the calves of the legs, especially the right and there was marked tenderness of the muscles of the right calf and in the right popliteal space, and slight tenderness over the same areas in the left leg From July 19 to 22 he complained also of pain and tenderness in both forearms July 26 Severe coughing attacks throughout night August 6 Pain in left side of chest August 17 Two severe chills August 18 Tenderness and palpable cord in right femoral region and in popliteal space and swelling of tissues of calf August 19 Suddenly developed labored respiration with cough and blood streaked expectoration These symptoms continued until August 22 when he died No autopsy

CASE 28—A M, female, aged 25 No 178,318 Admitted July 29, 1911. Patient had been ill for four weeks but had not gone to bed On admission the dilated and tortuous superficial veins on the inner and anterior aspects of both legs and thighs were thrombosed, dark in color and tender to pressure August 7, the patient suddenly became restless and dyspneic, complained of pain in the chest, and, later in the day, showed at the base of the right axilla, an area of diminished breathing over which were many fine râles The pulmonary symptoms continued, the signs remained unchanged and three days later the patient died No autopsy

CASE 29—B, male, aged 21 No 178,517 Admitted Aug 10, 1911, on sixth day of disease Very mild initial course After temperature had been normal for nearly five weeks it began, September 27, a step-like ascent, accompanied by general malaise and pains in the back and limbs October 4 Tenderness over right femoral and popliteal veins and pain in calf October 8 Had restless, sleepless night and complained of pain in chest No cough The signs of phlebitis gradually disappeared The fever lasted a considerable period There were no further pulmonary symptoms

#### PHLEBITIS WITH PULMONARY SYMPTOMS OF DOUBTFUL NATURE

CASE 30—P, male, aged 22 Admitted Nov 20, 1897 Pulmonary signs at one base, with rise of temperature after defervescence One month later frank signs of bilateral femoral phlebitis

CASE 31—H, female, aged 26 Admitted Dec 9, 1897 Pulmonary signs at right base late in disease Rise of temperature and rapid pulse Three weeks later phlebitis of right femoral vein

CASE 32—H W L, male, aged 35 No 5,341 Early pulmonary symptoms (severe cough and blood-streaked, frothy sputum) Later extensive phlebitis of both legs and right arm

CASE 33—C S, female, aged 23 No 8,695 Slight early pulmonary symptoms, probably not embolic Two weeks later phlebitis of left femoral vein

CASE 34—D E D, male, aged 24 No 13,097 After defervescence sudden cyanosis followed by rise of temperature and pain in region of diaphragm on left side Five days later phlebitis of right external saphenous vein

CASE 35—G S B, female, aged 20 No 14,095 Very severe course, patient delirious much of the time Between July 19 and 26 troublesome cough with slight expectoration July 26, 6 a m, sudden cyanosis and collapse July 28, "very free expectoration" July 29, "Complains of toes being painful" August 12, temperature after having been normal for five days, began to rise August 14 Troublesome cough August 17 Pain in right leg above foot August 29 Severe pain in left leg, with rise of temperature Later signs of phlebitis in both legs

CASE 36—A W, female, aged 28 No 16,313 During fifth week troublesome cough with râles, especially at right base Two chills Ten days later phlebitis of left femoral and calf veins

CASE 37—J T, male, aged 32 No 176,408 During defervescence troublesome cough for two days Five days later signs of left femoral phlebitis with chill and high temperature

#### PULMONARY SYMPTOMS SUGGESTIVE OF EMBOLISM WITHOUT EVIDENT PHLEBITIS

CASE 38—M K, female, aged 24 No 2,045 Admitted March 13, 1899 Average uneventful course At end of defervescence sudden, severe pain in right side of chest Three days later severe pain in toes of both feet, lasting several days No other signs of phlebitis

CASE 39—J D, female, aged 53 No 2,807 Admitted Aug 31, 1899 Normal and uneventful course until September 24 then at 2 a m sudden collapse with rapid breathing, weak pulse and cold sweat Gradual improvement October 1

sudden, severe pain in left side of chest, requiring morphin. Next day, dulness, bronchial breathing and crepitant rales over lower part of left lung behind. Signs disappeared in five days. October 8, severe pain in right hypochondrium. October 18, severe pain in right side of chest, lasting several days. Temperature up during each of the pulmonary attacks. No notes indicating phlebitis.

CASE 40—A P, female, aged 32. No 2,888. Admitted Sept 18, 1899. During fourth week chill, and on following day dulness, bronchial breathing and many rales over right lower lobe posteriorly. Two more chills on next day. Three days later sudden death. No mention of phlebitis. No autopsy.

CASE 41—S N, male, aged 19. No 4,567. Admitted Oct 7, 1900. Severe, protracted course. Temperature reached normal November 9. Rose abruptly November 15, without apparent cause and remained up for several days. December 1, chill with rise of temperature to 106 F, down next day. December 3, two chills. December 5, sharp pain in right side of chest, cough and many fine rales at right base and in lower part of right axilla. Pain, cough and pulmonary signs lasted for ten days. Temperature high and irregular for some days longer and then fell gradually. No mention of phlebitis.

CASE 42—J N, male, aged 34. No 6,355. Admitted Oct 7, 1901. Ran a moderate course, the temperature reaching normal on October 20, and remaining so until October 23. On this day it rose somewhat. On the next it reached 103 F, and there was pain referred to the upper part of the abdomen. On October 25 the pain was localized in lower part of left axilla and a pleuritic friction rub was present. October 28, chill. October 29, temperature still high, troublesome cough and signs of a small area of consolidation near spine of left scapula. On the following day most of these signs had disappeared. Temperature reached normal on November 4. No mention of phlebitis.

CASE 43—T C, male, aged 26. No 8,233. Admitted Sept 30, 1902. General condition good, lungs clear. On twentieth day (October 5) pain in left side of chest and friction rub. Two days later signs of fluid. Turbid, serous fluid removed from left chest. More fluid removed on October 10 and 12. October 13, 5 p m, patient died, apparently suddenly and unexpectedly. No autopsy. No mention of phlebitis.

CASE 44—E N, male, aged 26. No 8,480. Admitted Nov 20, 1902. Late in the disease sudden pulmonary signs with cough and bloody sputum. Then a "relapse," during which there were several chills and sweats. No notes indicating phlebitis.

CASE 45—K E, female, aged 43. No 8,872. Admitted Jan 31, 1903. Developed typhoid while in hospital. On thirteenth day (March 22) cough, expiratory grunt and small area of dulness above angle of left scapula. Several days later signs of consolidation at right base. Some time later, after temperature had reached normal, had a "relapse" with slight rise in leukocytes (10,000) but no notes to indicate presence of phlebitis.

CASE 46—R R, female, aged 26. No 9,115. Admitted March 14, 1903. Severe but uneventful course. Temperature reached normal April 18. One week later temperature rose again without discoverable cause. Leukocytes 9,000. May 4, sudden onset at night of severe pain in left hypochondrium. This pain lasted several days and was made worse by deepening breathing or coughing. The fever continued for some days after subsidence of the thoracic symptoms. No other indications of phlebitis.

CASE 47—W K, male, aged 27. No 9,979. Admitted Oct 3, 1903. Fairly severe course. On eighteenth day (October 5) sudden, severe pain in right axilla, followed next day by friction sounds in the same region. These signs lasted for ten days. Gradual defervescence. No notes indicating phlebitis.

CASE 48—E B A, female, aged 19. No 10,002. Admitted Oct 7, 1903. Moderate course. Temperature had been almost normal for several days when on

October 18, it rose again and ran a high and irregular course for some weeks  
 October 20 Severe pain in right side of chest and many fine râles in axilla  
 Next day cough and bloody sputum Leukocytes 19,000 October 25, still spit-  
 ting up blood Signs of consolidation in right interscapular region October 26  
 Sudden collapse with pallor, feeble pulse, etc October 27 Severe pain in right  
 upper quadrant of abdomen, with coarse friction rubs at base of right lung Cough  
 and bloody sputum November 9 Severe pain in *left* side abdomen, with pleuritic  
 râles in left axilla Cough with occasional bloody sputa continued some days  
 longer Eventual recovery No notes to indicate phlebitis

CASE 49—C W, female, aged 24 No 10,181 Admitted Nov 27, 1903 Mild  
 course By December 5, temperature had fallen to about 100 F December 6  
 Sudden pain in back, difficulty in breathing and rise of temperature The next  
 day the pain had become localized in left side of chest and was intense Temp  
 105 F, respiration 48, pulse 140 Leukocytes 13,000 December 8 Bronchial  
 breathing and voice over upper part of left lower lobe, with dullness, diminished  
 breathing and fine râles at the base By December 11, the signs of consolidation  
 had disappeared and the general condition was much improved Two weeks later  
 patient began to have small, bloody, mucous stools with much pain and tenesmus  
 (thrombosis of hemorrhoidal veins?) No other indications of phlebitis

CASE 50—J L, female, aged 16 No 13,337 Admitted Dec 28, 1905 Fairly  
 severe course Troublesome cough for several days during fifth week Later an  
 apparent relapse and during this, signs of pleurisy with effusion at left base No  
 leg symptoms

CASE 51—J R L, female, aged 28 No 13,373 Admitted Jan 4, 1906  
 Very severe course Late in the disease signs of consolidation in right lower lobe,  
 with chills and marked leukocytosis Rapid resolution No leg symptoms

CASE 52—L I male, aged 38 No 13,440 Admitted Jan 19, 1906 Mild  
 attack January 25 Began to have burning pain starting just below and inside  
 left shoulder and extending down forearm to hand, with inability to flex  
 thumb and index finger From February 6, to February 13, profuse sweats every  
 night February 15 Sharp pain in right side of chest on breathing, with dry  
 râles on inspiration The temperature after being normal for a week began to  
 rise on January 31 and remained elevated for three weeks The pain in the arm  
 lasted for several weeks

CASE 53—A M, female, aged 22 No 14,128 Admitted July 18, 1906  
 Moderate course At end of fourth week, with temperature almost normal, pain,  
 and signs of dry pleurisy in left side and rise of temperature Ten days later  
 (August 10) signs of dry pleurisy at base of right lung August 13, sudden  
 severe pain in left side of chest and left shoulder, with a few crepitant râles in  
 left axilla No further symptoms Rapid recovery No notes indicating phlebitis

CASE 54—L G, female, aged 25 No 14,211 Admitted Aug 10, 1906 Mod-  
 erate course and long relapse Toward the end of this signs of consolidation at  
 base of right lung Death No autopsy No indications of phlebitis

CASE 55—W M, male, aged 18 No 14,528 Admitted Nov 2 1906 Mod-  
 erate course At end of fourth week, with temperature low but unsteady, symp-  
 toms of severe plastic pleurisy at base of right lung which lasted for one week  
 No notes indicating phlebitis

CASE 56—H S, male, aged 21 No 14,625 Admitted Nov 26, 1906 Fairly  
 severe course During third and fourth weeks signs and symptoms of plastic  
 pleurisy over lower half of right chest Temperature reached normal about Decem-  
 ber 24 and remained so until January 1, when it rose suddenly to 104, remained  
 high for several days and gradually fell to normal No apparent cause for the  
 rise No notes indicating phlebitis

CASE 57—S Q male, aged 25 No 14,830 Admitted January 21 1907  
 Severe protracted course At end of fourth week (January 28) with temperature  
 falling, sudden very severe pain in right chest with rise of temperature and signs



of consolidation in right interscapular region. No change in leukocytes (7,000). Temperature reached normal February 2, and remained down until February 7. It then rose rapidly to 104 F, remained high for one week and gradually fell. Later there was another transient rise. Nothing found to explain the temperature. No notes indicating phlebitis.

CASE 58—I M, male, aged 16. No 14,903. Admitted Feb 8, 1907. Moderate course, uneventful until February 19, at which time temperature had fallen almost to normal. Then sudden pain in left chest. A few hours later had a chill with moderate rise of temperature. Four days later when temperature had again become normal, dulness at left base with rales. Two days later sudden transient rise of temperature to 105 F without apparent cause. Rales persisted for some days. No signs of phlebitis.

CASE 59—E P, female, aged 26. No 15,174. Admitted April 3, 1907. Severe course. On twentieth day (April 10) dulness, bronchial breathing and voice and crepitant rales over both lobes posteriorly. Signs lasted one week. Defervescence by lysis. No material rise in leukocytes. Slow convalescence. No signs of phlebitis.

CASE 60—A B, male, aged 27. No 15,514. Admitted June 18, 1907. Rather mild course. Temperature reached normal on June 28, and remained so until July 2. Then pain in right axilla, cough and "brownish viscid sputum" with rise of temperature. Later signs of fluid. After temperature had reached normal it rose again for a day or two without evident cause. No signs of phlebitis.

CASE 61—C A H, male, aged 32. No 17,579. Admitted Oct 31, 1908. Moderately severe course. Temperature gradually fell to normal and remained down for four days, then (November 24) began to rise. Pain in left side, and dulness, diminished breathing and friction rubs at base of left lung. Signs of pleurisy and cough lasted two or three weeks. Temperature fell gradually. No notes indicating phlebitis.

CASE 62—M H, male, aged 40. No 18,820. Admitted Sept 23, 1909, on eleventh day of disease. Complained of pruns in legs before admission. Slight pretibial edema. Uneventful course until October 20. Temperature running below 101 F. Then rise of temperature and pain in lower part of left chest with, later, pleuritic friction rubs over same region. No signs of phlebitis.

CASE 63—G P, male, aged 24. No 179,816. Admitted November 5, on twenty second day of illness. Severe course, uneventful until November 15. Then sudden pain in right axilla, followed by friction sounds, cough and abundant 'frothy, blood streaked sputum'. November 20. Pain and friction sounds now in *both* axillae. Cough and bloody sputum persisted. Temperature continued high and irregular. Two weeks later signs of small pulmonary abscess in left lower lobe. Operation. Death. No autopsy. No evidence of phlebitis.

#### THE RELATION OF THE LATE MULTIPLE CHILLS OF TYPHOID TO THROMBOPHLEBITIS

In studying the cases of typhoid with a view to ascertaining the mutual relations between phlebitis and pulmonary and pleural complications, it soon became evident that in the cases complicated by phlebitis the occurrence of chills was so frequent as to call for investigation, more especially as in most cases such chills were multiple. These multiple chills of the later weeks of typhoid have never received a satisfactory explanation. After eliminating the rare instances of true malarial chills and those seen in the course of pyelitis and other recognizable complications there remain a considerable number of cases of protracted typhoid

in which the latter weeks of the course are punctuated by a succession of abrupt violent rises of temperature, associated usually with chills and followed often by sweats. For these disturbing symptoms usually no adequate cause can be found, and, although the blood-cultures are uniformly negative and the leukocytes frequently show no significant change, these obscure cases are apt to be regarded as instances of post-typhoid sepsis. A further characteristic feature of these cases, in my own experience, is that they all ultimately recover.

Among the total number of cases of typhoid fever reviewed, multiple chills occurred in twenty instances. In sixteen of these twenty cases (80 per cent) there were well marked signs of thrombophlebitis. In every one of the four cases in which no signs of phlebitis were observed there were pulmonary symptoms strongly suggestive of pulmonary embolism (see Cases 40, 41, 44 and 51). In ten of the sixteen cases with phlebitis, also, there were symptoms of pulmonary embolism. Sometimes the chills would coincide with the onset of the pulmonary symptoms, occasionally they would synchronize with a fresh exacerbation of the phlebitis, but frequently they occurred without other symptoms and without apparent reason. In seven cases all the chills occurred before any of the signs of phlebitis were apparent. Four of the cases have already been cited (Cases 2, 9, 24 and 36), the others follow.

CASE 64—C G, male, 26 years old. No 8,488. Admitted Nov 22, 1902, on sixth day of illness. Moderate course. By November 27 temperature had fallen to 100 to 102 F. This continued until December 3 when temperature began to run higher. Chills occurred on December 7, 8, 10, 11 and 12. On December 31 patient complained of pain in calf of right leg and three days later there was tenderness over the calf, in the popliteal space and over the upper portion of the femoral vein. The temperature which had been about normal for some days began to rise on January 1 and remained elevated for two weeks. Meantime there were symptoms of extensive phlebitis of the right thigh and leg with, ultimately, slight edema. No pulmonary symptoms.

CASE 65—C K W, male, aged 48. No 12,626. Admitted June 21, 1905, on fifteenth day of disease. Fairly severe course. Between July 1 and 4 there were five chills, occurring without known cause, and during this time the leukocytes ranged between 4,000 and 5,300. On July 7 the right leg became painful and swollen and there was tenderness over the course of the femoral vein. On July 12 the left leg became similarly involved. No further chills, no pulmonary symptoms.

CASE 66—J V, male, aged 16. No 17,160. Admitted July 19 on seventh day of illness. Moderately severe course. On July 22 and 23 severe intestinal hemorrhages. On July 24, 25 and 29 chills without apparent cause. August 2 "Lungs clear except for scattered râles." Course uneventful until August 23 when there appeared signs of phlebitis in left groin. These later involved the left leg and were associated with edema. No pulmonary symptoms.

In six instances the chills took place both before and during the obvious manifestation of phlebitis. Cases 3, 6 and 13, and the following.

CASE 67—J H J, male, aged 24. No 2,634. Admitted July 26, 1899 on twentieth day of disease. Severe course. Very sick and delirious for a number of days. Between July 31 and August 15 there were six chills. On August 17

symptoms of phlebitis appeared in left leg and a few days later in the right leg. Further chills occurred on August 27 and 29 and September 2 and 6. The phlebitis ran a long, severe course. No notes of any pulmonary complications.

CASE 68—O H, male, aged 32. No 4,110. Admitted July 4, 1900, on fourteenth day of disease. Moderate course. July 15 chill with rise of temperature to 105 F. During next three days gradual fall in fever to 100 F, then (July 19) chill and rise to 105 F. After that the temperature continued high for some days. July 23, pain and tenderness over upper part of left internal saphenous vein and five days later signs of involvement of femoral on same side. Between July 24 and 31 five further chills. Slow convalescence. No pulmonary symptoms.

CASE 69—R R, female, aged 20. No 12,894. Admitted Aug 29, 1905, on sixth day of disease. Fairly severe course. September 13 (Nurse's note) "Complains of pain in feet. Left foot and ankle considerably swollen." From September 13 to October 1 patient had almost daily chills without obvious cause. Blood cultures were sterile, there was no rise in the leukocytes and physical examination of the chest was negative except for scattered sibilant and sonorous sounds. On September 19 a tender, elongated mass could be felt over the upper part of the left femoral vein and there was slight edema of both ankles. The symptoms soon subsided and it was not until October 25, after the patient had been sitting up for a few days, that frank symptoms of milk leg appeared. No pulmonary symptoms.

In three cases the chills did not occur until after the phlebitis had declared itself (Cases 21, 23 and 25).

In view of the fact that, in 80 per cent of the cases of typhoid marked by the occurrence of multiple chills of unknown cause, there was present also thrombophlebitis, and of the further fact that in all of the few remaining cases, in which no phlebitis was recognized, there occurred symptoms suggestive of pulmonary embolism, it is difficult to escape the conclusion that these obscure 'post-typhoid' chills bear some very direct relation to the thrombotic process in the peripheral veins. Just what that relation is, in every case, it may not be easy to say. Such rigors are probably not always due to the same cause. It is not uncommon for a chill to accompany the onset of symptoms of phlebitis of a large vein or to mark the sudden extension of such a phlebitis, but these are usually only single chills and this explanation fails entirely to account for the very characteristic type of cases we are considering in which chills may have been occurring almost daily for two or three weeks before any symptoms of phlebitis have appeared. A good many of the chills occurred simultaneously with the onset of symptoms of pulmonary embolism but in these same cases some of the chills would take place *without* such pulmonary symptoms, and the question arises as to whether a rigor may not at times be the only recognizable symptoms of the lodgment of a tiny embolus. Gerhardt,<sup>12</sup> in his classical description of the hemorrhagic infarct says "The act of embolism can pass almost or quite without symptoms when small fragments of clot enter a sound lung or where marked dyspnea already exists." He also speaks of a chill as a

<sup>12</sup> Gerhardt. *Der hämorrhagische Infarkt*. Volkmann's Saml. klin. Vortr. 1877, No. 91.

frequent symptom of embolism. Even on the assumption, however, that some of the chills which appear without accompanying pulmonary symptoms may be due to tiny emboli, the problem does not seem to be altogether solved, for occasionally a case is met with in which, although there are many chills, there are no pulmonary symptoms with any of them. It seems very unlikely that twelve or fifteen attacks of pulmonary embolism should occur without some of them presenting characteristic symptoms or physical signs. For such cases it must be acknowledged that there is, at present, no satisfactory explanation.

The literature contains a good deal of evidence in support of the view that the late, multiple chills of typhoid bear some constant relation to thrombophlebitis, although this relation appears never to have been fully recognized. The reason for this seems to lie in the fact that the chills often begin two or three weeks before the usual symptoms of phlebitis appear. Herringham<sup>13</sup> recorded six cases of multiple chills. In four of these the existence of thrombosis was recognized and in one other the symptoms as described strongly suggest thrombosis. Saw<sup>14</sup> reports two typical cases of "septic" chills, in both of which there was venous thrombosis and in one also, a late and severe pulmonary embolism.

Leclerc<sup>15</sup> and Howland<sup>16</sup> each report a case of multiple chills accompanied by thrombophlebitis.

Thayer<sup>3</sup> found that in 28 per cent of his cases of venous thrombosis complicating typhoid there were chills, and adds "In the past two years I have seen in consultation three further cases in which otherwise unaccountable chills during convalescence from typhoid fever were followed by a complicating thrombosis."

#### THE RELATION OF THE SYMPTOM OF "TENDER TOES" TO THROMBOPHLEBITIS

The study of the cases of phlebitis complicating typhoid fever brought out the further fact of the frequent association of such cases with the interesting symptom known as "tender toes." This condition of painful and exquisitely tender toes is, as is well known, an occasional complication of typhoid and always appears late in the disease or during convalescence. It is commonly regarded as a neuritis of the plantar nerves although, in many instances, the transient character of the symptoms, as well as the lack of trophic changes, suggests that the process can

13 Herringham. On Rigor and Collapse in Typhoid Fever. St Bart's Hosp Rep, 1896, LVII, 107.

14 Saw. Septic Phlebitis and Thrombosis of the Femoral Vein Complicating Typhoid Fever. Med Press and Circ, 1897, LXIV, 453.

15 Leclerc. Fièvre typhoïde, etc, Lyon méd, 1889, LXXI, 289.

16 Howland. A Case of Typhoid Fever with Repeated Chills. Med News, 1904, LXXXV, 820.

hardly be an actual neuritis. Among the 1,540 cases of typhoid reviewed this complication is recorded twenty-two times. In twelve of these cases (55 per cent) there was also the complication of phlebitis of the legs. In seven of the cases the tenderness of the toes was complained of before the appearance of the symptoms of phlebitis, in five cases the signs of phlebitis appeared first. Nine of these twelve instances of the association of tender toes with manifest phlebitis have already been cited (Cases 4, 5, 7, 12, 22, 24, 25, 35 and 69). The remaining three are given below.

CASE 70—F B, male, aged 21. No 1,278. Admitted Oct 4, 1898, on tenth day of disease. Average course. Temperature reached normal October 28. On October 20 first complained of "tenderness of toes." Allowed up in chair on November 2. Next day pain in left leg and on following day pain, tenderness and swelling in left calf. No temperature with the phlebitis.

CASE 71—F P S, male, aged 37. No 11,735. Admitted Dec 8, 1904, on fifteenth day of disease. Moderate course. Temperature fell rapidly to 100 F on December 24, then rose slightly for five days, then fell to normal. From December 27 to 31 patient had pain and tenderness in left foot and toes. January 2 signs of phlebitis in left thigh and calf.

CASE 72—P E C, female, aged 19. No 17,290. Admitted Aug 19, 1908, on tenth day of disease. Temperature reached normal by August 27. On August 30 the temperature rose slightly and remained somewhat elevated for several days. On August 31 there was severe pain in the left groin and upper part of thigh with all the usual symptoms of femoral and popliteal phlebitis. For the period of a week after the onset of these symptoms there was pain and tenderness in the sole of the left foot, toes and heel.

In addition to the above-mentioned cases of tender toes there were several cases of phlebitis in which pain and tenderness of the heel were the first indications of phlebitis in that leg.

#### TENDER TOES WITHOUT SIGNS OF PHLEBITIS

An analysis of the ten cases of tender toes in which there was none of the usual evidences of phlebitis shows that in seven of these there was at the time of the appearance of the painful and tender toes an irregular and unaccountable post-typhoid febrile movement. In one of the three remaining cases there were the symptoms of pulmonary embolism.

CASE 73—W H S, male, aged 24. No 1,043. Admitted Sept 5, 1898. Severe course. Temperature reached normal on September 20. On September 22 began to complain of severe pain and tenderness of feet and toes which lasted for some days. September 24, temperature rose to 102 F and fell to normal next day. Later patient ran a high and irregular temperature for twelve days, with no apparent cause.

CASE 74—M K, female, aged 24. No 2,045. Admitted March 13, 1899. Average course. Temperature reached normal March 26. On March 24 sudden pain on right side of chest. March 27 and for several days thereafter pain and tenderness of toes of both feet. No temperature. No notes indicating phlebitis.

CASE 75—F K B, male, aged 32. No 6,278. Admitted Sept 26, 1901. Protracted but not severe course. Temperature reached normal by November 4. On October 29 there was noted "pain and tenderness along the course of both internal plantar nerves especially the left." No evidence of phlebitis.

CASE 76—B E, male, aged 28 No 6,307 Admitted Oct 1, 1901 Protracted course Two early and small hemorrhages On October 14, first complained of tenderness of feet, especially on pressure Between this date and November 17 there are several references to the continued tenderness and pain in the feet On the nights of November 4 and 5 there were severe paroxysms of coughing On November 26 there were local applications to the legs—apparently because of pain After October 16 the temperature ran a high and irregular course On October 23 there was a sudden rise to 106.8 F It reached normal first on November 11 but did not remain constantly so until November 30

CASE 77—B B, female, aged 44 No 6,374 Admitted Oct 11, 1901 Short, mild course On admission "slight edema of the extremities" Between October 21 and 24 severe pain and tenderness in toes and soles of both feet No further symptoms

CASE 78—M S, male, aged 24 No 7,800 Admitted July 14, 1902 Moderate course Defervescence complete by August 4 On August 11 began to have pain and tenderness in toes of right foot which lasted eight or nine days With this there was a slight rise of temperature for three days No other symptoms

CASE 79—B S, female, aged 22 No 9,828 Admitted Aug 22, 1903 Long, severe course Severe bronchitis during the early weeks On September 6, first complained of tenderness of toes September 8, slight edema of feet and tenderness low in the right iliac fossa but no tenderness over either femoral vein The pain and tenderness in the toes was present almost constantly for the next two months The temperature which had gradually fallen to about 100 F began on September 17 to rise again and then ran a high and irregular course for the next six weeks without any local symptoms

CASE 80—C G F, male, aged 30 No 12,904 Admitted Aug 31, 1905 Course of average severity During convalescence and with normal temperature complained for several days of tenderness of toes No rise of temperature No other symptoms

CASE 81—G, male, aged 14 No 9,668 Admitted July 10, 1903 Fairly severe course On twenty-third day first complained of soreness of toes and soles of feet The tenderness and pain was very troublesome for four days and then disappeared Later a short "relapse" No other signs of phlebitis

CASE 82—C E, female aged 20 No 10,858 Admitted May 6, 1904 Mild, initial attack, followed by severe, prolonged relapse During this complained of tenderness of toes and feet Following this, prolonged, irregular, but not high temperature No notes indicating phlebitis

From the foregoing facts one is, of course, not justified in accepting as proven the causal relation between phlebitis and the symptoms of tender toes, and yet the association of the two conditions is much too frequent and striking to warrant the assumption that this association is merely a fortuitous one It seems unlikely that thrombosis and inflammation of the small veins of the foot should of themselves produce the symptoms under discussion It seems to me more probable that there is first a thrombosis of one or more of the veins in the region of the heel and that the subsequent periphlebitic exudate may in some cases be sufficient to irritate, or actually to cause, an inflammation of, the adjacent plantar nerves A moment's reference to any good anatomical plate of the deeper structures of the sole of the foot will show how very close is the approximation of the two plantar arteries, with their respective comities to the corresponding internal and external plantar nerves

Especially at the heel, where the posterior tibial artery, with its veins, curves over the astragalus to reach the sole of the foot, the vessels and nerves are in very close contact. There also it seems likely that the angular bend in the veins may predispose to the development of thrombosis and phlebitis. This hypothesis receives clinical support from the fact that pain and tenderness of the heel are not uncommon symptoms in thrombophlebitis.

It seems to me quite possible that some or most of the cases of *localized* neuritis which complicate typhoid fever may be found to be due to periphlebitic inflammation from some adjacent thrombosed vein, for in all the extremities the deep vessels and nerves are generally found in close proximity to each other. In Case 9 of this series, in which there was phlebitis of the left femoral and popliteal veins, there was evidently an associated neuritis, as shown by the weakness of the anterior tibial group of muscles in the affected leg.

#### THE TEMPERATURE IN THROMBOPHLEBITIS

A febrile movement of some degree was present in all but about 10 per cent of the cases of thrombophlebitis. In a majority of the cases the temperature rose with the appearance of the signs of thrombosis of a large vein. Not infrequently, however, the febrile movement began several days or even longer before any of the usual symptoms of thrombosis had appeared. Every possible variation, as regards time of appearance, duration, severity, type, etc., was encountered, in studying the behavior of the temperature in the cases of typhoid complicated by phlebitis. In a number of the cases there was fever for some days preceding the appearance of signs of phlebitis, but no fever afterward. In others the temperature rose only after the phlebitis had been manifest for several days. The vagaries of the temperature curve are well shown in the cases cited in the section relating to multiple chills. In a good many of the cases after the period of typhoid defervescence had become nearly or quite complete the temperature would rise again and then run a long and irregular course, in the midst of which, at some time, appeared the signs of venous thrombosis. Sometimes this post-typhoid fever was accompanied by chills, sometimes there were sudden, short rises of temperature without an accompanying chill and without apparent cause.

Such late and prolonged periods of fever are often regarded as relapses or recrudescences of the typhoid process, but it is not difficult I think to distinguish between a true relapse and the type of fever under consideration. In going over the temperature charts of a large number of cases of typhoid I have been led to the conviction that in all uncomplicated cases of typhoid the fever curve is strikingly uniform and constant in its general type although varying much in its duration, its

severity, and to some extent, in the length of its periods of ascent and defervescence. Any radical departure from this familiar type usually indicates the existence of some complication, even though the complication may not always be readily discoverable. The same statements, I believe, apply to the true and uncomplicated relapse. There is the more or less gradual ascent, the period of continuous elevation and the period of defervescence, and the chart of such a true relapse bears little or no resemblance to the various types of post-typhoid temperature described above. Sudden, violent remissions or exacerbations; greatly prolonged, slight, febrile movements, the occurrence of chills, are all indications that the fever is not that of a true relapse, but is due to some complication or sequel. In such cases, when the various other possible complications have been excluded, there will usually be found sooner or later some symptoms to indicate the existence of a thrombophlebitis. Many of the sudden and transient rises of temperature seen during convalescence from typhoid and usually ascribed to errors in diet are unquestionably due to this cause. The fact that a febrile movement may have existed for two or three weeks before any signs of phlebitis of a large vein have appeared cannot be held to invalidate this view as to the association of the two conditions, for there is an abundance of evidence to show that the phlebotic process may remain latent, or nearly so, for a period of several weeks.

No entirely satisfactory explanation for the occurrence of fever in the course of a latent phlebitis can be given at present. Bock<sup>17</sup> has recently shown by experiments on animals that the intravenous injection of some indifferent and sterile substance, such as paraffin, in a finely divided state, is regularly followed by some rise in temperature. It is possible that some of the elevations of temperature seen in the early stages of phlebitis may be caused by the separation of tiny fragments of the thrombotic material before the vein has become occluded. Whatever may be the true explanation, the fact is beyond question.

Vaquez,<sup>7</sup> speaking of the behavior of the temperature in phlebitis, says "We believe, for our part, that very frequently a notable elevation of temperature precedes the appearance of *phlegmasia alba dolens*, but that this elevation of temperature should be sought for not on the day, or the second day, before the first apparent manifestation, but often eight, ten or twelve days before."

#### THE LEUKOCYTES

In most of the cases there was some rise in the number of leukocytes, and some increase in the proportion of the polynuclear cells, at the time of the appearance of frank signs of phlebitis of a large vein. The

17 Bock. Ueber Fiebererscheinungen nach intravenösen Injectionen vornehmlich indifferenter Partikelschen. Arch f exper Path u Pharm, 1912, lxxviii, 1



increased leukocyte count varied from 10,000 to 26,000. In some cases there was no appreciable rise in the leukocytes at any time, and in many cases a leukopenia persisted for some time after the appearance of the first indications of involvement of the veins. The absence of a leukocytosis cannot, therefore, be used as evidence against the existence of venous thrombosis. The increase in the leukocytes seems to depend chiefly on the presence of a well-marked periphlebitis.

In the present article it has been my aim, not to cover every possible symptom and complication of thrombophlebitis as it is seen in typhoid fever, but to call attention to several interesting groups of symptoms not usually regarded as having any direct relation to venous thrombosis, and to attempt to demonstrate that such a direct relation does actually exist. But this study of the late complications of typhoid in relation to venous thrombosis brought to light a number of interesting and suggestive facts whose significance is not yet clear, and which have not been discussed here, but which, nevertheless, are worthy of study and elucidation. Indeed, it is hardly too much to say that the whole symptomatology of the later weeks of typhoid requires to be studied anew from the standpoint of the possible relation of the various symptoms to thrombophlebitis. For example, the relation of thrombosis of the veins of the mesentery and of the intestinal wall to the abdominal symptoms of typhoid is altogether unknown. The fact that in the routine, post-mortem examination of typhoid cases such thromboses are rarely if ever discovered, is by no means proof that they do not occur. Thrombosis of the smaller veins could readily pass unrecognized unless special attention were directed to their examination. In reading through the protocols of the cases complicated by phlebitis I have been struck by the frequency with which various obscure abdominal and intestinal symptoms occur. It is possible that some of the attacks of sudden abdominal pain, tenderness and distention which often closely simulate the symptoms of perforation, that some of the dysenteric symptoms, that some of the repeated, small intestinal hemorrhages, may have their origin in thrombosis of the small mesenteric veins.

Two other late complications of typhoid may be mentioned as being worthy of investigation as to their possible connection with thrombophlebitis. One is periostitis, which appeared in a number of the cases during the course of a phlebitis. The other is the rare complication of inflammation of the breasts. In a woman with thrombosis of the veins of the legs there appeared first in one breast and then in the other a phlebitis of one of the veins near the periphery, which was followed by an extensive periphlebitis so that the condition might easily have been mistaken for a primary mastitis. One cannot but wonder if in all the

instances of so-called mastitis complicating typhoid the process may not have begun as a thrombosis of the mammary veins

#### SUMMARY

The opinions set forth in the preceding pages may be briefly summarized as follows

1 Thrombophlebitis is a much more frequent complication of typhoid fever than is generally supposed, and probably occurs in from 10 to 15 per cent of all cases. Its development is gradual, its course frequently latent for many days, and its classical symptoms usually appear only at a late stage of the condition. The thrombotic process is apt to be much more extensive and more widely disseminated than the pronounced local symptoms would suggest.

2 Most of the pulmonary and pleural complications which appear late in the course of typhoid are due to embolism of branches of the pulmonary artery, and this in turn is due to a complicating venous thrombosis. Such emboli are usually small and their symptoms are frequently mild and transient. The emboli seem to arise chiefly from the freshly formed, friable thrombi in veins which have not yet become occluded, and their symptoms, in a majority of the cases, appear before the usual symptoms of phlebitis are observed.

3 The obscure, late, recurring chills of typhoid are regularly associated with venous thrombosis although the latter is frequently latent at the time of the appearance of the chills. Some of the chills are certainly related to the lodgment of pulmonary emboli.

4 The symptom of "tender toes" can be shown to be associated with thrombophlebitis, in a majority of the cases. The suggestion is made that this symptom may be due to irritation or inflammation of the plantar nerves, which is set up by periphlebitic inflammation from adjacent, thrombosed veins in the sole of the foot or about the heel.

5 Many of the unaccountable rises of temperature seen during convalescence from typhoid and most of the protracted and irregular types of "post-typhoid" fever are due to thrombophlebitis.

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# THE PEPTOLYTIC POWER OF GASTRIC JUICE AND SALIVA WITH SPECIAL REFERENCE TO THE DIAGNOSIS OF CANCER

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## I

In 1909 Neubauer and Fischer inaugurated the use of the dipeptid, glycytryptophan, for the detection of peptid-splitting power in stomach contents, with special reference to the diagnosis of carcinoma. Their report called forth a shower of comments. It is not necessary to give a detailed account of the work, since this has been done repeatedly. But it may be recalled that it was based on an idea of Friedrich Muller that stomach contents from carcinoma patients could carry protein cleavage beyond the point at which normal peptic digestion ceases, and that this power was due to the presence in cancer tissue of an enzyme which could be secreted into the stomach.

Emerson showed that malignant growths actually contain an enzyme capable of splitting protein beyond the albumose phase, and in greater strength than that seen in benign growths, normal tissues, or in blood. He found similar properties in gastric contents from cancer patients. This work was confirmed and extended by H. Fischer, and Neubauer and Fischer, who introduced the dipeptid glycytryptophan as a reagent for the detection of peptid-splitting enzymes, and applied it in the study of a series of clinical cases which included twelve of carcinoma. The test consists in mixing glycytryptophan with gastric juice, incubating the mixture and testing with bromin for the rose-violet color indicative of free tryptophan. They drew the following conclusions: 1. In carcinomatous stomach contents a ferment occurs, which, unlike pepsin, splits glycytryptophan. 2. The ferment is destroyed by 0.36 per cent hydrochloric acid. 3. The presence of the ferment is usable in diagnosis ("*ist diagnostisch verwendbar*"). Since certain later writers have asserted that the test has no diagnostic value, we call attention to the conservative wording of the original.

In the examination of contents from pathological stomachs they recognized, *a priori*, certain sources of error: 1. Occurrence of tryptophan in the stomach contents themselves. 2. Presence of peptid splitting bac-

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\* From the Otto S. A. Sprague Memorial Institute Laboratory of Clinical Research, Rush Medical College.

\* Manuscript submitted for publication Sept. 2, 1912.

teria 3 Presence of trypsin (pancreatic juice) 4 Presence of blood (elepsin).

Concerning *tryptophan in stomach contents as aspirated*, much had already been written by Erdmann and Winternitz, Glaessner and Volhard. The conclusions of these writers, confirmed by Neubauer and Fischer, were to the effect that tryptophan seldom occurs in normal cases, that it frequently occurs in carcinoma and at times in certain non-malignant conditions associated with low acidity, and in motor insufficiency even with high acidity. Neubauer and Fischer regard such contents as unsuitable for application of their test. Concerning *the influence of bacteria* they conclude that simple filtration of the contents through paper is a sufficient safeguard. *Reflux of pancreatic juice* interferes with the test, but since, save in cases of cessation of the outflow of bile, it seems hard to imagine reflux of intestinal contents into the stomach without bile, they advise testing for bile and discarding such specimens as contain it.

By the latter part of 1911 seven communications had appeared commenting on this work (Lyle and Kober, Ley, Kuttner and Pulvermacher, Weinstein, Ehrenberg, Oppenheimer and Pechstein). None of the writers attacked the principle of the test. All applied it to series of cases. All agreed that it was positive in most cases of cancer and negative in most normal cases. The reaction was observed, however, in non-malignant conditions associated with sub- or anacidity, and found negative in some cases of cancer. There was a manifest divergence of opinion as to the exact limits of its usefulness.

Lyle and Kober, Oppenheimer, and Pechstein reported in the main favorably, Weinstein objecting to the cost and stability of "*ferment diagnosticum*" (the commercial toluenized solution of glycytryptophan marketed by Kalle & Co., Biebrich a. R.), held that a direct bromin test for tryptophan in the stomach contents was simpler and more reliable than the glycytryptophan procedure. In so doing he reverted, apparently unconsciously, to the older idea of Volhard and Glaessner. He disagreed with Neubauer and Fischer on minor points, but came to generally favorable conclusions, especially as regards the direct test for tryptophan after a protein meal. Kuttner and Pulvermacher also objected to the use of glycytryptophan on the score of cost. They proposed using silk peptone instead and gauged its splitting by the observation of a precipitate of tyrosin under the microscope. They made eight parallel tests to establish the equivalence of the two procedures, and then discarding the glycytryptophan method, made a series of observations with silk peptone. From the results so obtained they came to highly unfavorable conclusions. They coincide with the views of those who regard reflux of pancreatic juice as a common occurrence, and consider

the bile tests recommended by Neubauer and Fischer as inadequate for its exclusion. Ley and Ehrenberg had unfavorable experiences.

In a second communication published in 1911, the original writers review the literature up to that time. They point out that Kuttner and Pulvermacher employed a test differing from their own without adequately establishing the interchangeability of the two. Their analysis of the results obtained by all the above-mentioned writers indicates that out of all definitely proven cases of carcinoma studied, 84 per cent, and of the clinically diagnosed, 75 per cent, had shown positive reactions, while of the non-cancerous cases 14 per cent were positive. They reiterate their cautions concerning blood and add that serum will also split glycytryptophan, in illustration of which they cite a case of uremic gastritis in which a positive test was encountered. They disclaim ever having entertained the view that the test was in any sense specific. With the possible exception of the Bence-Jones albumose reaction in myeloma, clinical chemical tests are not generally to be so regarded. However, they maintain that when properly performed and considered in conjunction with other data, this procedure is, as originally claimed, an aid in diagnosis.

In the meantime other reports have appeared (Hall and Williamson, Warfield, Koehlker and Sanford and Rosenbloom). Hall and Williamson find positive reactions in most cases of cancer but not in all. They also find some positive reactions in non-cancerous conditions and suspend their judgment. Warfield, working with saliva obtained from the mouth with no aseptic precautions, and relying on the use of toluene and sometimes centrifugation for exclusion of bacterial action, finds that saliva mixed with a solution of glycytryptophan and incubated splits the latter, to give a positive tryptophan reaction with bromin. He suggests the possibility that bacteria may be responsible for this, but drops it with a negatively tending reference to Weinstein, and Neubauer and Fischer. Acids inhibit this action. The less acid in the stomach contents, according to Warfield, the greater the frequency of positive reactions, in benign as well as in malignant conditions. On the other hand definitely cancerous contents with high combined acidities or with a relatively large amount of lactic acid are said to yield negative tests. He points out that although the presence of a peptid-splitting enzyme in cancer juice seems to have been demonstrated (and one may add in strengths greater than that of normal tissues including blood), the fact that carcinoma of the stomach is so often accompanied by absence of free hydrochloric acid, makes it "just the condition most favorable for a continuance of the salivary action", then in concluding says "In view of these facts the glycytryptophan test is of no value in the diagnosis of cancer" (!) Koehlker working from a theoretical standpoint with other di- and tripeptides whose splitting he detects with the polariscope, finds that all

are hydrolyzed by saliva under experimental conditions similar to those used in Warfield's work. He is conservative in ascribing these effects to non-bacterial enzymes, but in view of the universal presence of ereptases in the tissues is inclined to the view that the peptid-splitting power of saliva is inherent.

In a second article Weinstein states that saliva is incapable of splitting Witte peptone. (As demonstrable by the bromin test for tryptophan.) Sanders and Rosenbloom disagree with this observation. From our own results it would appear that saliva as obtained from the mouth and protected with toluene frequently splits Witte peptone sufficiently to cause a marked increase in the formol-titrable nitrogen. Within twenty-four hours of incubation, however, we have not so far encountered positive tryptophan reactions. As regards the use of the glycytryptophan test for cancer diagnosis, Sanders and Rosenbloom endorse the position taken by Warfield, that it is worthless.

## II

Having now presented the salient features of the literature, certain general observations may be made.

The principle that carcinoma tissue contains an enzyme capable of splitting polypeptids and in greater strength than is found in normal tissue, blood and non-malignant new growths, has not been disputed. All agree that in a large majority of the cases of gastric carcinoma, the stomach contents show the power to hydrolyze polypeptids. So far the possibility of devising a suitable procedure for detecting the cancer enzyme for diagnostic purposes would seem as great as it ever was. But the practical application of the glycytryptophan procedure for this purpose has yielded inconstant results in the hands of different workers, some normal cases, many cases with low acidity and a few other non-malignant conditions, have reacted positively, some cases of definite carcinoma have reacted negatively. Although some writers, expecting too much from an organic chemical reaction, have gone too far in depreciation of the test, it must be conceded that the greatest indefiniteness in results has been observed among the very group of cases in which the suspicion of carcinoma is justified by already existing methods, and among which differentiation is most to be desired. A non-malignant case with low acidity is likely to react positively, an early carcinoma developing on an ulcer base with high acidity is likely to be negative.

In deciding just how valuable the test is it makes a great deal of difference how we explain these variations, the variations which occur in spite of precautions such as Neubauer and Fischer recommend. If reflux of pancreatic juice into the stomach without the presence of readily detectable bile is a frequent phenomenon, as held by Kuttner and Pulvermacher in accordance with the view of Boldeyreff and others, then the

test loses much of its value and no change in the details of its application will be likely to restore it. The pathologic-physiologic basis will have been undermined. If, as the work of Warfield and Koehlker appears to indicate, saliva possesses an enzyme which hydrolyzes polypeptids, the test in its present form falls to the level of a mere index of conditions in the stomach favorable for continuance of salivary digestion. Conceivably some means might be developed for eliminating these sources of error by controlling the reactions of the stomach contents or otherwise, but this is problematical. If, on the other hand, inconsistencies in the test are due to imperfections in the details of the method of applying principles which are correct, one might hope to eliminate the objectionable features.

Concerning the two most serious criticisms, that of Kuttner and Pulvermacher and that of Warfield, it is interesting to note that they are in part opposed to one another. One explains positive reactions in cases with low acidity by entrance of saliva through the cardia, the other by entrance of pancreatic juice through the pylorus. Both cannot be entirely right. If the reactions seen are due solely to saliva they are not due to pancreatic juice, and *vice versa*. The only ground for agreement would be the compromise that both processes are concerned.

Now there is no doubt that saliva as obtained from the mouth does in many cases contain something which has the power to cleave polypeptids. We have repeatedly confirmed this observation with glycytryptophan and with Witte peptone.\* It is equally certain that saliva passes normally into the stomach. Then given conditions in the stomach favorable for a continuance of this action and it follows that peptid splitting must occur there for this reason alone. In view of this consideration it is clear that the mere demonstration of polypeptid splitting power in gastric juice carries with it no proof of any second enzyme entering from the pylorus. Unless there are other proofs that pancreatic juice may gain access to the stomach than the mere detection of peptid splitting, or until such splitting is observed under conditions which preclude the effect associated with saliva, one is not warranted in the assumption that any reflux of pancreatic juice actually occurs. For the combined effects of pepsin and saliva are equal to the effect of trypsin. Boldyreff, Kuttner and Pulvermacher and others, have never excluded this source of error and the burden of proof lies with them.

Let us now consider more in detail the question of saliva. If pure sterile saliva contains an enzyme which can split peptids, the test has a limited value. If the observed splitting is due to bacteria, it is less serious obstacle. We have tested the action of saliva before and after passage through a Berkefeld candle and *have never seen any peptid splitting power in the filtered secretion, although it was frequently observed in the unfiltered samples*, and again in the filtered, after these

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\*In some samples of saliva however, we have failed to demonstrate any peptolytic power.

had been inoculated with a mere loopful of the former. The process of filtration did not impair the amylolytic power of the saliva and we feel safe in the assertion that *non-filterable bodies in the saliva are responsible for its apparent peptid splitting action*. These non-filterable bodies are here regarded as bacteria, although some have suggested the possibility of a selective filtration of enzymes. Theoretically it would make no essential difference as to the effects which are seen in the stomach contents whether the action were bacterial or due to a secreted enzyme. The same chemical conditions might favor either, and on the other hand, high acidities, whether due to HCl or to an unusual quantity of lactic acid, would check bacteria as well as the enzyme. Warfield's results might be interpreted in this way as well as in another. All are familiar with the inhibition of the growth of certain bacteria in milk or in the bowel by the predominance of lactic acid bacilli and their product. Practically it is certain that whatever gives saliva its peptolytic power this can be effectually eliminated by mechanical means. Toluene is not free from objections.

Since heretofore no greater precautions have been taken in the study of peptolysis in stomach contents than in saliva, it is obvious that unless the conditions in the stomach are such as to check bacterial action already begun the same remarks apply here as have just been made for saliva concerning the chances of confusing bacterial action with that of native enzymes. Especially when there are infected teeth, gums or tonsils, and catarrhal processes in the nasopharynx or ragged ulceration in the gastric mucosa itself, will the chances for bacterial action be great. The experiments made by Neubauer and Fischer to determine how much attention should be paid to bacteria did not exclude the possibility that a heterogeneous mass of organisms in such culture media as may occur in subacid stomach contents, may actively split peptone. Nor is the simple filtration through paper, which they recommend, a reliable safeguard against this source of error. Papers vary, some are fairly effective, others not.

Up to this point, then, we find no basic objection to their test but see in the inadequate provisions for excluding bacteria one explanation for disagreement among different observers. There are also other points to be considered. When gastric juice is mixed with a solution of glycyltryptophan and the cleavage of the latter is detected by application of a bromin test, we end with a delicate and easily-masked color reaction—a purely qualitative test permitting scarcely a guess as to the extent of the splitting. Even then we are dealing solely with *the cleavage of a single dipeptid*. A given stomach content might cleave other peptids in greater quantity in one case, less in another. The substitution of Witte peptone or silk peptone for glycyltryptophan introduces a theoretical difference even though in the end we gauge the cleavage by testing qualitatively for a single end-product. If we use Witte peptone and rely on the bromin test as an index of its splitting, we fail to observe any



cleavages except those which in the end liberate free tryptophan, hence considerable hydrolysis of this substance can occur before a positive bromin test is obtainable. The same applies to the use of silk peptone and observance of the tyrosin precipitate. On the other hand, a positive test implies a whole succession of hydrolyses which have carried the peptone down to its simplest components. For this very reason peptone may be a more suitable substance to use for clinical purposes. Theoretically glycytryptophan should be a more delicate reagent than peptone under these conditions, because it cannot split at all without giving the substance (tryptophan) used as the index. Possibly it is too delicate for clinical purposes.

The greatest consistency in results might be expected from a quantitative method which would tell us the total peptid splitting power of a given gastric juice, acting under definite conditions for a definite time on a uniform mixture of polypeptids. Such a test should give us a set of figures from which to draw conclusions as to the amount of splitting which is to be regarded as normal, what the limits for the normal are, how much splitting power a positive qualitative tryptophan test corresponds to, how much splitting can occur in the non-malignant diseases, how much in cancer, etc. Such relative figures based on a series of observations naturally would not be regarded as absolute, but they should enable us to classify stomach contents on the basis of polypeptid splitting power in the same way that we now compare them on the basis of acidity.

For this purpose we have used a 2 per cent aqueous solution of Witte peptone which is mixed with gastric juice and subjected to formol titration in accordance with the method of Ronchèse-Malfatti-Sorenson. After titration of a 10-c.c. sample of the mixture the remainder is placed in the incubator and after twenty-four hours retitrated. The excess of peptone by combining any free acid which may be present makes further neutralization unnecessary.

In applying this method in a series of cases, we have aimed especially to ascertain (1) whether normal gastric juice and saliva split peptone at all, and, if so, to what extent, (2) how much of the peptid-splitting power which has been observed in saliva, and in gastric juice of non-malignant diseases, is due to bacteria, and whether, if the action of bacteria is certainly excluded, there still remains in such gastric juices any splitting power which would have to be ascribed to reflux of pancreatic juice unaccompanied by bile, (3) how much of the peptid splitting seen in cancer cases is due to bacteria and how much is due to other causes (e.g., cancer enzyme), (4) the value in diagnosis of the quantitative method as compared to that of simply testing for tryptophan in the Witte peptone, gastric juice mixtures after incubation and in general the

diagnostic value of any method for detecting polypeptid or peptid splitting power in gastric juice <sup>1</sup>

### III

The results obtained may be summarized as follows

Saliva as obtained from the mouth, filtered simply through paper and incubated under toluene, often but not always has the power to split Witte peptone and glycytryptophan. But if the saliva is filtered through a Berkefeld candle and kept aseptic, all detectable peptolysis disappears. The same is true for its power to split glycytryptophan. If the aseptic peptone-saliva mixture be inoculated with a drop of unfiltered saliva, peptolysis again occurs (Table 1)

The peptolytic power of gastric juice (and blood) has been estimated in terms representing the increase in the number of c c of N10 KOH required in the formal titration of 100 c c gastric juice (or serum) with 200 c c 2 per cent Witte peptone solution after twenty-four hours incubation at body temperature. This figure, here designated as the *peptolytic index*, is used for comparisons.

The peptolytic index for pure, fresh blood-serum from healthy individuals was found to average 8, part of the rise being due to autolysis of the serum itself.

For normal gastric juice as studied in forty cases, the minimum was 0, maximum 18, average 10.5, or about that found for serum. In none of the forty cases was there a positive color test for tryptophan before or after incubation with peptone solution (Table 2)

In ten cases of hyperacidity the minimum index was 0, maximum 6, average 6 (lower than the normal) (Table 3)

In twenty-two cases of subacidity and anacidity in which the free HCl ran from 10 to 0, total acidity 20 to 5, the maximum peptolytic index was 33, minimum 0, average 9 (Tables 4 and 5)

The indices, then, were lowest in hyperacidity, a little higher in the normal, a little higher yet in some of the stomach contents from cases of an- and subacidity. For this entire group of seventy-six normal and non-malignant cases the inverse relationship between acidity and pepto-

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<sup>1</sup> We had intended also to compare the results obtained by the Neubauer and Fischer method with those obtained by simple substitution of Witte peptone for glycytryptophan, and those of the quantitative method herein described. But at the time this work was begun (some two years ago) we had trouble in obtaining "ferment diagnosticum". We regret, therefore, our inability to state whether in a long series of cases substitution of Witte peptone for the dipeptid is more or less advantageous except by comparing our results with the published results of others. Such comparison suggests that Witte peptone is less likely to yield a positive result in non-malignant conditions and equally reliable in cancer cases. Perhaps glycytryptophan for reasons already mentioned, is too sensitive. The peptone is also cheaper.

lysis as observed for glycyltryptophan by Warfield, seems to hold good. Tryptophan reactions were, however, uniformly negative.

One case of non-malignant stenosis gave a positive tryptophan reaction with bromin. In this instance stomach contents were examined on three different days. The indices ran 0, 7 and 9, average 5.3, or well within the normal limits. This shows the possibility of encountering now and then a positive color reaction with what may be regarded as a "normal" peptolytic power. It explains possibly some of the discrepancies in results obtained by qualitative methods. Since theoretically "*ferment diagnosticum*" should show free tryptophan to the bromin test with a slighter peptid splitting power than with peptone, for reasons already given (p. 566) it may well be that this dipeptid is even more likely than peptone to give a positive result with a normal case.

Four of the samples in the subacidity series which showed the highest peptolysis were filtered through a Berkefeld filter and mixed with peptone solution under aseptic conditions. In cases so treated the index always became 0. (Table 5, Cases 113, 114, 115, 117.) This observation, together with the point previously mentioned, that in non-malignant cases peptolysis and acidity are in an inverse relationship, indicates that in these benign cases, peptolysis is due to bacteria whose action is inhibited by acid.

Twenty-three cases of cancer have been studied from which thirty-three samples of gastric juice were obtained (Tables 6 and 7). In all cases the diagnosis was made at operation or at autopsy. Six of the malignant series were cases of carcinoma developing on an ulcer base, with free HCl between 15 and 20, total acidity 60 to 70 (Table 6, last six cases). In this group, in spite of acidities above those of the non-malignant cases, the indices ran, maximum 72, minimum 48, average 69, i. e., the minimum index is once and a half that of the maximum found in forty normal and thirty-six non-malignant subacidity cases. The tryptophan reaction after incubation with Witte peptone was positive in all. These findings do not confirm the views of Warfield that peptolysis is due to a salivary enzyme which fails to act when the acidity is high. Twelve of the fourteen cancer cases with free HCl 0, and total acidity between 5 and 10 (Table 7), gave indices as follows: maximum 165, minimum 63, average 98.5, i. e., the least index was twice as great as the maximum non-malignant figure encountered, while the maximum was five times as great. The average was nearly ten times that of the normal average (10.5).

The qualitative tryptophan test was positive in thirteen of the fourteen, and failed in one case (Case 75) in spite of the low acidity and the excessive peptolysis shown by titration. Two of the fourteen cancer cases

(Table 7, Cases 60 and 86) gave indices not so greatly exceeding the highest non-malignant figures

In four cases doubt had existed as to the diagnosis. In each of these the free HCl and total acidity were 5 and 15, respectively (by coincidence). The peptolytic indices by the antiseptic method averaged 148, minimum 120, maximum 165. The tests in this series were also made by the aseptic method (filtration through a Berkefeld candle and subsequent use of sterile pipettes and flasks without toluene). The indices then averaged 97.5, maximum 105, minimum 87. Peptolysis was reduced by the filtering, but only moderately so and remained on the average nearly ten times as high as the normal average, even when for the latter we take the figures of the toluene method. Exploratory operation was made and revealed carcinoma in each case (Cases 99, 112, 120, 122, Table 7).

TABLE 1—TESTS WITH SALIVA

Saliva, 1 part, sterile peptone solution, 2 parts. Of the mixture 10 c.c. subjected at once to formol titration, a second 10 c.c. incubated for twenty-four hours with addition of acid or alkali as indicated under remarks. A indicates that toluene was used for antisepsis, B, that the saliva was filtered through a Berkefeld filter and handled aseptically. The table shows comparative effects of toluene and filtration, also the high peptolysis when neither is used.

## — Formol Titration —

No of Ex- per	Before Incuba- tion	After Incuba- tion	Rise	Br Test	Remarks
I	15	20	05	0	A No addition of acid or alk
II	11	21	10	0	A Made alkaline to litmus
III	10	13	03	0	A Made alk to phenolphthalein
IVa	09	11	02	0	A Added N/10 to make 18%
IVb	09	11	02	0	A Added N/10 to make 36%
IVc	09	10	01	0	A Added N/10 HCl to make 18%
Va	11	13	02	0	A No addition
Vb	11	72	61	0	Same with toluene omitted
Vc	11	11	00	0	B No addition
VI	14	14	00	0	B No addition
VIIb	14	25	11	0	Same reinfection with fresh saliva
VII	45	45	00	0	B No addition

In one case the contents were obtained at autopsy. By the usual method of examination with filtration through paper and incubation under toluene, the index was 186, with no toluene added it was 219, after filtration through porcelain without using toluene, 129, showing the inhibiting effect of toluene to be less than that of filtration. The figures obtained in the last five cases cited also show that neither filtration nor toluene, nor a combination of the two will eliminate the peptolytic power from certain cancerous stomach contents from which it is apparent that unlike what was found for benign and normal conditions, we have to do in cancer cases with two peptolytic fractions, viz, microorganisms and something filterable. The filterable peptolyzing agent might be regarded as an extracellular enzyme from bacteria or a ferment from cancer. Saliva and normal gastric juice and that from subacidity cases however.

TABLE 2—TESTS WITH GASTRIC JUICE—NORMAL CASES

Table made from the data obtained in forty cases No symptoms in any Free HCl, 30-40 Total acidity, 50-60 in all Bile, blood and lactic acid tests negative in all Table includes the extremes and averages of 40 cases

Case	—Formol Titration—			Br Test	Acidity		Remarks
	Before Incuba- tion	After Incuba- tion	Rise		HCl	Total	
65	6	12	6	0	30	58	Case which showed greatest peptolysis
121	5	5	0	0	39	56	Two characteristic cases with no demonstrable peptolysis
63	8	8	0	0	40	58	
Av	6	9.5	3.5	0	35	55	Averages from 40 cases

Peptolytic index Max 18, Min 0, Av 10.5

TABLE 3—TESTS WITH GASTRIC JUICE—HYPERACIDITY CASES

Ten cases, with HCl 50-80, total acidity 70-110 Bile, blood and lactic acid always absent and no sign of dilatation or obstruction Symptoms such as occur commonly in "hyperchlorhydria" with nothing to suggest, directly, ulcer or other organic stomach disease, (or, no symptoms, the hyperacidity having been discovered by routine)

Case No	—Formol Titration—			Br Test	Acidity		Remarks
	Before Incuba- tion	After Incuba- tion	Rise		HCl	Total	
3	3	3	0	0	60	70	Epileptic
14	2	2	0	0	60	75	
21	2	2	0	0	65	90	
32	2	2	0	0	70	98	
44	12	12	0	0	50	70	Morning aspiration
46	12	14	2	0	81	109	
48	10	10	0	0	56	76	
50	16	16	0	0	69	85	
41	15	15	0	0	63	111	
52	6	6	0	0	72	86	

Peptolytic index Max 6.0, Min 0, Av 6

TABLE 4—TESTS WITH GASTRIC JUICE—SUBACIDITY CASES, A

Ten cases with free HCl 10-15, total acidity 25-30 Bile, blood and lactic acid tests uniformly negative

Case No	—Formol Titration—			Br Test	Acidity		Remarks
	Before Incuba- tion	After Incuba- tion	Rise		HCl	Total	
23	8	8	0	0	12	25	Symptoms in these cases were mild, e g, anorexia, weight or distress p c with headache and neurasthenic symptoms Physical findings were negative, no ptoses, no dilatations, no motor insufficiencies In three cases diarrhea was present
24	15	15	0	0	8	15	
25	10	12	2	0	10	20	
51	10	13	3	0	10	26	
53	4	7	3	0	10	30	
64	9	13	4	0	5	12	
88	13	13	0	0	10	26	
100	7	10	3	0	12	15	
104	7	10	3	0	10	25	
54	9	15	6	0	6	24	

Peptolytic index Max 18, Min 0, Av 7.2

completely lose their peptolytic power with suitable filtration, from which it would appear that filtration is adequate for eliminating bacterial action. Others have shown that cancer tissues, aseptically prepared, do contain a peptolytic enzyme. Therefore it seems more plausible to ascribe the filterable agent to the cancer. Our own work, however, does not finally establish this point. Possibly a cancerous mucosa lodges bacteria which do not thrive under other conditions.

TABLE 5—TESTS WITH GASTRIC JUICE—SUBACIDITY CASES B

Sixteen cases Free HCl 0, total acidity 8 to 30. In four of these cases (113, 114, 115, 117) filtration was carried out through a Berkefeld filter with subsequent aseptic handling, and also by the usual paper filtration with subsequent antiseptic (toluene) treatment.

Case No	Formol Titration		Rise	Br Test	Acidity		Lactic	Bile	Blood	Remarks
	Before Incubation	After Incubation			HCl	Total				
40	9	12	3	0	0	8		0	0	Filtered through paper toluene added
62	15	17	2	0	0	10		0	0	Same as above
68	16	18	2	0	0	10	0	0	0	Same as above
70	6	13	7	0	0	12	0	0	0	Same as above
73	8	12	4	0	0	6	0	0	0	Same as above
95	12	16	4	0	0	10		0	0	Same as above
106	12	14	2	0	0	30	0	0	0	Same as above
109	5	8	3	0	0	30	0	0	0	Same as above
116	15	15	0	0	0	10	0	0	0	Same as above
111	16	17	1	0	0	12	0	0	0	Same as above
66	6	9	3	0	0	8	0	0	0	Same as above
71	7	18	11	0	0	22	0	0	0	Same as above
113	2	4	2	0	0	10	0	0	0	Same as above (Aseptic)
113	2	2	0							
114	15	17	2	0	0	10	0	0	0	Same as above (Aseptic)
114	15	15	0							
115	6	11	5	0	0	12	0	0	0	Same as above (Aseptic)
115	6	6	0							
117	12	21	9	0	0	10	0	0	0	Same as above (Aseptic)
117	12	12	0							

Peptolytic index Max 33, Min 0 Av 10.5, 16 cases (usual method)

Peptolytic index Max 0 Min 0 Av 0 4 cases (aseptic method)

Three cases of carcinoma showed indices of 0, 6 and 12, no higher than the benign series, and hence negative (Table 6, Cases 33, 87, 92). In one of these cases there was the high lactic acid content which Warfield found associated with negative glycytryptophan reactions, in the others the acidities were low. In all, 88 per cent of the cancer cases were positive by the quantitative method, 83 per cent by the qualitative. Of seventy-six non-malignant cases only one gave a positive tryptophan test.

In the series of cases here reported, the maximum index found in any of seventy-six benign cases by the toluene method was thirty-three, and this was seen in but one case. The minimum index in the cancer cases, barring three, was forty-five. For practical purposes we may say then that when reliance is placed on paper filtration and toluene

Indices of 0-20 are negative  
Indices of 20-40 are suspicious  
Indices of 40 and over are positive

TABLE 6—MALIGNANT CASES

Nine cases of carcinoma with free HCl, 0 to 20, total acidity, 5 to 70. Diagnosis confirmed in all but two obvious cases either at operation or at autopsy

Case No	Formol Titration			Bi Test	Acidity			Blood	Lactic	Remarks
	First	Second	Rise		HCl	Total	Bile			
33	12	14	2	0	0	6	0	0	++	Negative Cases. All were operated on. Cases 33 and 92 showed cancer at lesser curvature, Case 87 cancer at pylorus. Note low acidity in two cases.
87	12	12	0	0	0	36	0	0	++	
92	15	19	4	0	0	5	0	0	0	
118	*A M	17	40	23	+	10	30	0	0	Six cases of malignant disease with high total acidities, carcinoma of pylorus found at operation in each case. Marked rise in every case in spite of acidity.
		20	44	24		8	21	0	0	
37	A M	21	46	25	+	15	70	0	0	
		16	40	24		18	60	0	0	
61	A M	14	38	24	+	20	70	0	0	
		14	37	23		15	65	0	0	
81	A M	13	41	23	+	10	70	0	0	
		17	43	26		12	60	0	0	
82	A M	16	39	23	+	6	53	0	0	
		20	41	21		15	63	0	0	
83	A M	13	29	16	+	8	60	0	0	Peptolytic Index. Av 69, Max 72, Min 48
		14	38	24		15	60	0	0	

\* A M = Material aspirated in morning before giving test breakfast

There is no doubt that the significance of demonstrable peptolysis of even moderate degree, if observed in aseptic specimens, is much greater than that seen when it is necessary to allow leeway for bacteria and establish empiric borders. From the series of ten non-malignant cases in which we have filtered gastric juice through a Berkefeld filter all peptolysis has disappeared, and it is anticipated further work will show that any peptolysis which survives filtration of this sort is abnormal and likely to mean cancer, provided always that gastric juices containing bile be excluded. For accurate work the aseptic method should be used exclusively. It will be found most practical, perhaps, for ordinary clinical purposes to dispense with filtration in cases with very low and very high indices and apply it in case of uncertainty, i. e., when the figures are between 20 and 40.

It is also important to exclude bacteria when using the qualitative test, since those present in non-malignant cases will sometimes cause a positive reaction. It is possible also that an overgrowth of certain forms, such for instance as lactic acid bacilli, may be responsible for a negative result in a cancer case.

TABLE 7—MALIGNANT CASES

Fourteen cases of carcinoma with free HCl, 0 to 20, total acidity, 5 to 70. Diagnosis confirmed in all but two obvious cases either at operation or at autopsy.

Case No	Formol Titration			Bi Test	Acidity			Blood	Lactic	Remarks
	First	Second	Rise		HCl	Total	Bile			
86	2.2	4.0	1.8	+	0	5	0	0	+	Clinical diagnosis — cancer — confirmed at operation
93	2.1	4.2	2.1	+	0	5	0	0	+	Obvious mass, metastases, cachexia, death, no autopsy
101	2.2	4.6	2.4	+	0	5	0	0	+	Clinical diagnosis of cancer confirmed at operation
102	2.2	4.4	2.2	+	0	5	0	0	+	Clinical diagnosis of cancer confirmed at operation
37	2.2	4.5	2.3	+	0	5	0	0	+	Clinical diagnosis of cancer confirmed at autopsy
58	2.4	4.6	2.4	+	0	5	0	0	0	Clinical diagnosis of cancer confirmed at autopsy
60	2.2	3.7	1.5	+	0	10	0	0	0	Clinical diagnosis of cancer confirmed at autopsy
75	2.1	5.1	3.0	0	0	10	0	0	0	Clinical diagnosis of cancer confirmed at autopsy
76	2.2	5.2	3.0	+	0	10	0	0	0	Epigastric tumor, nodular liver, cachexia, no autopsy
84	1.9	4.0	2.1	+	0	8	0	0	?	Clinical diagnosis of cancer confirmed at autopsy
99	1.5	7.0	5.5	+	0	5	0	0	+	Clinical diagnosis, "suspicious" carcinoma at operation
99†	1.5	5.0	3.5	+						
112	1.5	7.0	5.5	+	0	10	0	0	+	Clinical diagnosis, doubtful; operation — death, autopsy — carcinoma
112†	1.5	4.4	2.9	+						
120	1.5	5.5	4.0	+	0	5	0	0	+	Clinical diagnosis doubtful. Operation showed posterior wall carcinoma with glandular and hepatic metastases
120†	1.5	4.8	3.3	+						
122	1.3	6.2	4.9	+	0	6	0	0	+	Clinical diagnosis of cancer confirmed at autopsy
122†	1.3	4.3	3.0	+						

† Aseptic method

Peptolytic index: antiseptic (toluene) method. Max 165, Min 45. At 105.

#### CONCLUSIONS

1. Saliva free from bacteria does not split Witte peptone nor glycyL-tryptophan.

2. Normal gastric juice free from blood, bile (trypsin) and bacteria has no peptolytic power. The same holds true for cases of benign sub-acidity.



3 Peptolytic and peptidolytic action exhibited by saliva, and so-called "tryptic" digestion in the stomach when there is no bile to indicate reflux of intestinal contents, are usually due to unfilterable agents (bacteria)

4 There is no incontestable evidence to show that pancreatic juice unaccompanied by bile ever gains access to the stomach (except in cases with acholic intestinal contents)

5 Toluene is inadequate for the exclusion of bacterial action in experiments with saliva and gastric juice

6 In about 88 per cent of developed cases, carcinomatous stomach contents show a peptolytic power two to ten times the maximum seen in benign conditions in general This is due in part to bacteria, but high peptolysis persists after filtration through a Berkefeld and subsequent aseptic handling

7 Witte peptone may be advantageously substituted for "*ferment diagnosticum*" in the Neubauer and Fischer qualitative test, with results in malignant cases as good as any that have been published for glycyl-tryptophan itself In non-malignant cases it has been positive but once in seventy-six normal and *Subacid* cases

8 The quantitative method herein described yields slightly more uniform results than the qualitative procedure in cancer cases It has never been found "positive" in seventy-six normal and non-malignant cases

9 The detection or measurement of peptolytic power in gastric juice, if carried out by any suitable method, is of considerable value in the diagnosis of cancer

10 It is of value in any case, and essential in doubtful cases, to eliminate bacteria by passage of the gastric juice through a Berkefeld or other equally effective filter, with subsequent aseptic precautions

#### IV—EXPERIMENTAL

##### MATERIAL

*Saliva* was obtained from different members of the laboratory staff The mouth was rinsed with water and the flow promoted by masticating a bit of paraffin Samples from different individuals were used in some experiments, mixtures in others The material was filtered through paper or through a Berkefeld candle as indicated on the charts

*Stomach contents* were obtained by aspiration one hour after a test breakfast consisting of 30 gm bread and 200 cc water In most instances the stomach was emptied in the morning prior to giving the test breakfast, and the results of both aspirations examined Unless specified on the charts as "morning aspiration" the material is understood to have been obtained after a test breakfast In one case the material was obtained at autopsy Each sample was subjected to a test for bile (dilute alcoholic iodin), for blood (Weber), lactic acid (Uffelmann), and the usual routine titrations, with demethyl amido- $\alpha$ -benzol and phenolphthalein A direct test for tryptophan with dilute bromin water or bromin vapor was also made Samples giving positive bile or blood reactions or having a yellow or greenish color even in the absence of positive tests, were not used The material was filtered through a folded filter or a Berkefeld candle, or both, as indicated in the records

Cases were drawn from the Cook County and Presbyterian hospitals, Chicago, the dispensary of Rush Medical College, the private practice of Dr. Jacque and scattering sources. It has been necessary in some malignant cases to rely on the word of the operating surgeon for the final diagnosis, without histological examination. Cases of this sort which have been included have been operated on by surgeons of known competence. For help in obtaining cases, records and material, we are especially indebted to Dr. Donald Abbott, interne in Cook County Hospital. We also desire to acknowledge the support of Dr. Frank Billings, Dr. James B. Herick, Dr. A. D. Bevan, Dr. J. Davis and others, for use of material.

#### METHODS

*Peptone Solution*—A 2 per cent solution of Witte peptone is filtered through a folded filter, distributed in 60 cc flasks, sterilized in an autoclave and kept on ice. If the flasks are both cotton- and cork-plugged, the stock solution keeps its titer for a long time. One flask is used for each set of experiments.

#### PROCEDURE

**A (Antiseptic)** Ten cc gastric juice (filtered through a folded filter) are measured into a flask by means of a pipet. To this are added exactly 20 cc peptone solution and, after mixing, a layer of toluene is added. Exactly 10 cc of the mixture are withdrawn from under the toluene with a pipet and subjected to formol titration as follows. To the 10 cc of mixture add 50 cc  $H_2O$  and 5 drops of 1 per cent alcoholic phenolphthalein, then N/10 KOH to the first permanent pink tint. Take 5 cc liquor formaldehydi diluted with 10 cc water, add 5 drops phenolphthalein and neutralize in the same way. Add the neutral formol solution to the neutral peptone gastric juice mixture. The mixture becomes acid. Titrate back to the first permanent pink and note the number of tenth cubic centimeters required.<sup>2</sup>

**2 Note**—In using phenolphthalein as indicator and bringing to the first permanent pink both for the original neutralization and in the final titration, we intentionally disregard the criticism that for absolute values neutralization with litmus and a final titration to violet with phenolphthalein is preferable. These figures are purely relative and the use of phenolphthalein as proposed by Malfatti for the urinary  $NH_3$  is quicker and more satisfactory for this purpose.

The remaining 20 cc of peptone gastric juice solution (a) are placed in the incubator for twenty-four hours (stoppered) and at the end of this time 10 cc are withdrawn and treated as before. The first titration figure is subtracted from the second and the difference is an expression of the peptolysis which has occurred in a mixture of  $3\frac{1}{2}$  cc gastric juice with  $6\frac{1}{2}$  cc peptone solution ("Rise"). The rise multiplied by 3 and by 10 gives the figures for peptolysis in 100 cc gastric juice with 200 cc Witte peptone solution ("Peptolytic Index"). When sufficient material is available it is preferable to use double quantities of gastric juice and peptone solution for the titrations.

**B (Aseptic)** The gastric juice is passed through a sterilized kaolin filter (Berkefeld) and subsequently handled in sterile pipets and flasks which are plugged with both cotton and cork. No toluene is used.

*The qualitative test* is performed by simply adding cautiously to 5 cc of the solution to be tested a drop or two of dilute bromin water and observing the delicate rose or rose violet tint which occurs in presence of tryptophan.

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# THE RELATION OF THE VIRULENCE OF THE TUBERCLE BACILLUS TO ITS PERSISTENCE IN THE CIRCULATION

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Bacteria frequently gain access to the circulation. However, there is still a marked difference of opinion as to how frequently this occurs and how serious this invasion is, some believing that it is a phenomenon always accompanied by marked systemic disturbance, others that if the number of bacteria is small, the body rids itself of the invaders without the aid of any general reaction. It is known that microorganisms are eliminated from the circulation chiefly by way of the kidneys and of the liver, but it is not known what the determining factors are. Are the bacteria filtered from the blood stream by means of the tissues, in the same way as inert foreign particles, for example, as would be the case if an equal amount of egg white had found its way into the blood, or does this mechanical process play a rôle secondary to other finer defensive processes?

The following investigation was undertaken primarily to obtain some answer to a simple question, to discover whether, quite independently of their power of multiplication, a direct relationship exists between the virulence of bacteria and their ability to maintain an existence in the circulation. It seemed as if the tubercle bacillus presented an unusual opportunity for a study of this nature. For, as is well known, the bovine type of tubercle bacillus is highly virulent for rabbits when a small fraction of a milligram is injected intravenously, whereas the human type of this bacillus is but slightly virulent, possessing the power of giving rise to merely local lesions in the lungs and in the kidneys, which do not disseminate the disease or result in the death of the animal. The two types of bacilli are almost alike morphologically, and multiply so slowly as to make this factor negligible in an experiment of short duration. Their chief and preeminent difference is that of virulence. A series of tests was therefore instituted, which, briefly stated, consisted in inoculating a measured quantity of human and of bovine tubercle bacilli into the circulation of rabbits, and of determining whether they persisted in the blood-stream for approximately the same length of time.

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The experiments were planned as follows. Four rabbits were injected for each test, two with a human type of bacillus, the other two with the bovine type, in each case 0.1 mg and 1 mg of a culture was suspended in a salt solution and injected into the ear vein. These four animals, which were of about equal weight, were bled at regular intervals, generally one-half hour, one hour, two hours and three hours after inoculation, 5 c.c. of blood being caught in a solution of sodium citrate. Thus there were eight specimens taken from the two rabbits inoculated with the human tubercle bacillus, and eight from the two inoculated with the bovine bacillus. These sixteen specimens of blood were immediately injected subcutaneously into as many guinea-pigs, and after six weeks these animals were examined for tuberculosis.

In addition to a series of experiments of this description, others were undertaken in which the rabbits were bled soon after inoculation, or after a period longer than three hours following the injection of the bacteria. Furthermore, it was possible to test the blood of a large number of rabbits which, in the course of various laboratory work, had been inoculated with bovine or with human tubercle bacilli, and to study, in this connection, the relation of bacteremia to the tuberculous condition of the animal—a subject which in the field of human pathology has been the center of much discussion during the past few years, and which we touched on only incidentally.

It will be seen from the accompanying table (Table 1) that six experiments, of the type which has been outlined, were successfully carried out. Others were undertaken, but owing to difficulty in bleeding the rabbits, to occasional clotting of the blood, to the premature death of some of the guinea-pigs, or to other unavoidable causes, they had to be altogether rejected.

The table shows our results more clearly than mere description. If we take the first experiment, for example, we find that of the eight pigs inoculated with the blood of rabbits injected with bovine tubercle bacilli, four showed tuberculosis when killed after an interval of six weeks, one died prematurely, so that three of the eight tests were negative. On the other hand, only one specimen of the eight taken from the two rabbits inoculated with the human culture incited tuberculosis in the guinea-pigs used for the tests. In this way the experiments may be interpreted. Table 2 brings out these results more clearly, and is a summary of all six experiments. Here we see that there were forty-four rabbits inoculated with a culture of human tubercle bacilli, and an equal number of successful inoculations with bovine culture. This includes all specimens of blood drawn at intervals varying from one-half to three or four hours after the rabbits were inoculated. Of the bovine tests eighteen were found to contain tubercle bacilli, that is, 59

per cent, whereas of the tests with human culture only four gave rise to tuberculosis in the guinea-pigs, that is, only a little over 9 per cent. It will be seen that there is some irregularity in the results, that at times bacilli were found in the circulation after two or three hours, although they were not demonstrable after shorter intervals. The difference between the two groups as shown in this table is, however, so marked that the conclusion is definite that the two types of bacilli, the markedly virulent and the feebly virulent, differ decidedly in their

TABLE 1—RELATIVE PERSISTENCE OF THE HUMAN AND THE BOVINE TUBERCLE BACILLUS IN THE CIRCULATION

Interval in hours between inoculation and bleeding	Amount and Type of Bacilli Injected into Rabbits				Remarks
	0.1 mg (B)	1 mg (B)	0.1 mg (H)	1 mg (H)	
EXPERIMENT I					
1	—	Tb	—	—	
2	—	Tb	Tb	—	
3	0	Tb	—	—	
4	Tb	—	—	—	
EXPERIMENT II					
1/2	—	—	Tb	—	Bovine culture was almost avirulent for rabbits
1	—	—	—	—	
2	—	—	—	0	
3	—	—	—	—	
EXPERIMENT III					
1/2	0	—	—	—	Suggests possible confusion between the two "bovine" rabbits
1	Tb	0	—	—	
2	Tb	—	—	—	
3	Tb	—	—	Tb	
EXPERIMENT IV					
1/2	Tb	Tb	—	0	Clot interfered with fourth test of first column and third test of third column
1 1/2	Tb	Tb	—	0	
2 1/4	Tb	Tb	—	0	
3 1/4	—	Tb	—	—	
EXPERIMENT V					
1/2	Tb	Tb	—	—	
1	Tb	Tb	—	—	
2	Tb	—	—	—	
3	—	Tb	—	—	
EXPERIMENT VI					
1/2	0	Tb	—	—	
1	Tb	Tb	—	—	
2	—	Tb	Tb	—	
3	Tb	Tb	—	—	

Tb = Tuberculosis of guinea-pig — = no tuberculosis, 0 = premature death, etc., B = Bovine, H = Human

ability to persist in the circulating blood. That this difference is intimately associated with virulence was further brought out by an experiment in which a bovine culture was used, which was almost avirulent for rabbits as the result of prolonged artificial cultivation (Table 1, Exper II). In this experiment, the bovine bacilli were not found in the circulating blood in any instance. Furthermore it must not be thought that the negative results of the various tests with the human culture

were attributable to its having lost its virulence for guinea-pigs, for a series of tests using from 0.01 mg to 0.00000001 (1/1,000,000,000) mg of culture proved that 0.0001 (1/100,000) mg incited a marked tuberculosis when injected subcutaneously

Table 3 is a record of bleedings of a rabbit made at various intervals for more than twenty-four hours after it was inoculated with 1 mg of a virulent bovine culture. It will be seen that these bacilli were still circulating in the blood twenty-seven hours after inoculation. In tests instituted one week to two months after inoculation with a bovine

TABLE 2—SUMMARY OF SIX EXPERIMENTS OF TABLE 1

Experiment	Bovine Tb		Human Tb	
1	4	3	1	7
2	0	8	1	6
3	3	3	1	7
4	7	1	0	5
5	6	2	0	8
6	6	1	1	7
	<hr/>		<hr/>	
	+	—	+	—
	26	18	4	40
	<hr/>		<hr/>	
Total No of cases	44		44	
Tb per cent	59		91	

+ = rabbit's blood contained tubercle bacilli

— = rabbit's blood did not contain tubercle bacilli

TABLE 3—PERSISTENCE OF BOVINE TUBERCLE BACILLI IN THE BLOOD (27 HOUR TEST\*)

Time of Bleeding	Interval after Inoculation, Hours	Guinea-pig Test	Time of Bleeding	Interval after Inoculation, Hours	Guinea pig Test
2 p m	2	Tb +	9 a m	21	Tb +
3 p m	3	Tb +	11 a m	23	Tb +
4 p m	4	Tb +	1 a m	25	Tb +
5 p m	5	Tb +	3 a m	27	Tb +

\* 1 mg of bovine culture in 1 c c of salt solution was inoculated into a rabbit. Five c c of blood tested

culture (Table 4 A), tubercle bacilli were found in six out of seventeen instances, and all six had been injected from one to two months previously. So that it would seem that there exists a period in which the blood is sterile, an intermediate period between the time when the bacilli originally inoculated are eradicated from the blood-stream, and when in the course of a progressive tuberculosis, bacilli once more gain access to the general circulation. Among twenty-three similar tests in which a culture of human tubercle bacilli was inoculated, producing, however, but slight or no tuberculous lesions, only two showed bacilli in the blood (Table 4 B). In one of these positive cases a careful post

mortem examination of the rabbit failed to reveal any tuberculous lesion, we regard the finding of bacilli in this instance as an interesting but chance occurrence.

TABLE 4—LATER TESTS OF INOCULATED RABBITS  
A BOVINE

No of Rabbit	Interval Since Inoculation Days	Amount of Blood Tested c c	Autopsy of Rabbit	Result of Blood Test
1148	7	7	Tb	Tb
1149	7	7	Tb (m)	Neg
1149	14	7	Tb (m)	Neg
1149	16	7	Tb (m)	Neg
1153	14	7	Tb (m)	Neg
1153	22	6	Tb (m)	Neg
1155	21	6	Tb	Neg
1155	29	6	Tb	Neg
1152	30	7	Tb	Neg
1100	30	4.5	Tb	Tb
1100	30	4.5	Tb	Tb
1127	30		Tb	Tb
1126	30		Tb	Tb
1126	42	5	Tb	Neg
1160	35	7	Tb	Neg
1159	60	10	Tb	Tb
1159	60	10	Tb	Tb

B HUMAN

1158	1	5		Neg
1109	17	3	Neg	Neg
1109	20	6	Neg	Neg
1110	17	3	Tb *	Tb
1110	20	6	Tb *	Neg
1110	60		Tb *	Neg
1105	17	3	Tb *	Neg
1105	20	6	Tb *	Neg
1104	17	3	Tb *	Neg
1104	24	6	Tb *	Neg
1107	17	3	Tb *	Neg
1107	24	6	Tb *	Neg
1103	17	3	Neg	Neg
1103	24	6	Neg	Neg
1108	17	3	Neg	Neg
1108	24	6	Neg	Neg
1118	30	5	Neg	Tb
1118	90	3.5	Neg	Neg
1118	90	10	Neg	Neg
1121	30	5	Neg	Neg
1121	90	3.5	Neg	Neg
1121	90	3.5	Neg	Neg
1161	30	7	Neg	Neg

m = Miliary tuberculosis The other rabbits had typical massive bovine tuberculosis  
\* Slight

It is difficult to form a satisfactory hypothesis to explain the mechanism by which bacteria are able to circulate hundreds of times within the blood-stream and persistently escape the tissue filters. The feebly virulent human type, as well as the bovine bacillus was regularly found in the blood from three to twenty minutes after inoculation (Table 5)



TABLE 5—EARLY BLEEDINGS OF INOCULATED RABBITS

Nature of Inoculation	Interval After Inoculation, Minutes	Amount of Blood Tested, c c	Result
Bovine (1 mg )	3	5	Tb +
Bovine (1 mg )	10	5	Tb +
Bovine (1 mg )	20	5	Tb +
Human (1 mg )	3	5	Tb +
Human (1 mg )	10	5	Tb +
Human (1 mg )	20	5	Tb +

TABLE 6—ANAPHYLACTIC SYMPTOMS FOLLOWING SUBCUTANEOUS INJECTION OF RABBITS' BLOOD

Condition of Rabbit	Amount of Blood Injected, c c	Anaphyl-actie Symptoms	Death	Remarks *
Bovine Tb	5	++	+	Died in ½ hr
Bovine Tb	5	—		
Bovine Tb	5	++	+	
Bovine Tb	5	++		
Bovine Tb	5	++		
Bovine Tb	5	++		
Bovine Tb	5	++	+	Died in 1½ hrs
Bovine Tb	5	++	+	Died in 1½ hrs
Bovine Tb	5	+		
Bovine Tb	5	+		
Bovine Tb	5	—		
Bovine Tb	3 5	++		
Bovine Tb	5 5	+		Blood in refrigerator over night
Bovine Tb	7	++	+	Death in 28 hrs
Bovine Tb	7	++	+	Blood in refrigerator nine days
Bovine Tb	7	++	+	Blood in refrigerator nine days
Bovine Tb	10	++		
Bovine Tb	14	++		
Human Tb	5	—		Rabbits almost free from tubercu- lous lesions
Human Tb	5	—		Rabbits almost free from tubercu- lous lesions
Human Tb	5	—		Rabbits almost free from tubercu- lous lesions
Human Tb	5	—		Rabbits almost free from tubercu- lous lesions
Human Tb	5	—		Rabbits almost free from tubercu- lous lesions
Human Tb	7	++		Rabbits almost free from tubercu- lous lesions
Human Tb	7	+		Rabbits almost free from tubercu- lous lesions
Normal	5	+		
Normal	5	—		
Normal	5	—		
Normal	5 5	—		
Normal	7	+		
Normal	7	+		
Normal	7	—		
Normal	7	—		
Normal	10	++		
Normal	10	—		
Normal	17 5	++		

\* Guinea-pigs weighed about 250 gm

It is possible that the bacilli cling to the walls of the vessels and the current of the circulation for considerable periods. However, of the lack of experimental data in this particular it is best to make hypotheses. This is likewise true in regard to efforts attempted to account for the difference in this respect between the virulent and comparatively avirulent types of tubercle bacilli. It is not attributable, however, to a difference in the opsonic power of the blood, tests we carried out, as well as those of others,<sup>1</sup> show that no clear distinction exists between the indices for the human and for the bovine type of tubercle bacilli.

In the course of the inoculation of rabbits' blood into guinea-pigs interesting toxic (anaphylactic) phenomena were frequently observed: abdominal distention, coma, spasm of the hind legs, scratching of the face and other symptoms of this complex which are well known. These symptoms have been described by others,<sup>2</sup> following intraperitoneal inoculation of rabbit serum, as well as local necrosis,<sup>3</sup> which, however, we did not encounter in the course of our many subcutaneous injections. It seemed to us as if the toxic symptoms were more frequent and more marked in instances in which blood was injected from rabbits suffering from bovine tuberculosis. Accordingly we undertook an extended series of tests, summarized in Table 6, to gain a clearer understanding of the reaction. It became evident that our impression was correct, that blood injected with normal blood or the blood of rabbits inoculated with a culture of the human tubercle bacillus reacted less regularly and with less intensity than did those inoculated with an equal amount of blood of rabbits suffering from tuberculosis of the bovine type. Guinea-pigs inoculated with the blood from the bovine rabbits frequently died with symptoms simulating anaphylactic shock. Serum stored in the refrigerator for some days retained this toxic property. The toxicity cannot be explained by the fact that in the one case we were testing the blood of a markedly diseased animal, and in the other that of an animal which was almost normal, for the blood of a guinea-pig suffering from rabies did not possess similar toxic properties. In connection it should be mentioned that Friedberger and Schuetz were unable to extract anaphylatoxin in the test tube from tubercle bacilli, adding normal guinea-pig serum and complement. The amount of toxin obtained varied according to the proportion of antigen, serum, and complement used, and the period of extraction. Our results

1 Koehlsch. Ztschr. f. Hyg., 1911, lxxviii, 193

2 Thomson, O. Ztschr. f. Immunitätsf., 1909, 1, 741

3 Pfeiffer. Ztschr. f. Hyg., 1897, xxv, 384

4 Friedberger, F. and Schuetz, A. Ztschr. f. Immunitätsf., 1911, ..

stitute a confirmation *in vivo* of these test-tube experiments, their lack of absolute regularity must be attributed to the variability of the diverse controlling factors

#### CONCLUSIONS

For an experiment such as we set ourselves, namely, to determine the relation of virulence of bacteria to their persistence within the blood-stream, the tubercle bacillus would seem to be especially suitable. Apart from the fact that it multiplies so slowly, that this factor is negligible in a test of short duration, it occurs in two types, one feebly virulent to rabbits the other highly virulent. Morphologically these bacteria are almost identical, their preeminent difference is one of virulence. Accordingly definite quantities of these closely related microorganisms were inoculated into rabbits, and bleedings were carried out from one-half to four hours later to discover whether bacilli were still circulating in the blood. In a series of tests of this nature it was found that the feebly virulent human type of bacillus was present in only 9 per cent of the tests, whereas the virulent bovine bacillus persisted in the blood-stream in 59 per cent of the cases. These results seem to warrant the conclusion that virulence plays an important rôle in bacteremia, and that the bacteria may not be filtered from the blood by the tissues like inert foreign bodies. The fact that an avirulent bovine strain did not persist in the circulation strengthened us in this conclusion.

It is remarkable for how long a period after inoculation bacteria may still be found in the general circulation. In one instance in which but 1 mg. of bovine culture was inoculated, these bacilli were constantly found in the blood at various intervals during the subsequent twenty-seven hours. A period intervenes some days after inoculation during which even the virulent organisms are not found in the blood. However, this constitutes merely an intermediate or latent phase, and is followed by another phase cycle, in which, owing to the tuberculous condition of the animal, there is a reinvasion of the general circulation. For example, in tests performed a week or two subsequent to inoculation no bacilli were found, whereas in tests repeated a month later, when systemic tuberculosis had developed, bacilli were frequently demonstrated. These generalizations are subject to exception, in the case of one animal, although tubercle bacilli were obtained from the blood, autopsy some weeks later failed to reveal any tuberculous lesion.

In the course of a large series of injections, the interesting and suggestive phenomenon was noted, that the blood of the highly tuberculous rabbit is more toxic for the guinea-pig than that of the normal rabbit.

## THE RELATION OF URICOLYSIS TO SUBOXIDATION

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The later investigations in purin metabolism have disclosed the fact that there are clearly defined differences between man and other animals with respect to the ultimate products of the disintegration of the purin nucleus. In all mammals, man excepted, uric acid undergoes oxidation prior to excretion, so that in the dog, for example a large part of the preformed uric acid is found in the urine as allantoin. Likewise in those mammals that excrete allantoin in appreciable amounts, it has been possible to demonstrate in the organs, usually liver and kidney, an enzyme that is capable of destroying uric acid—uricase. Up to the present all efforts directed toward disclosing uricase in man have met uniformly with negative results, and Wiechowsky has shown that if uric acid is destroyed at all in the human body it can hardly be by oxidation since the diurnal allantoin excretion averages only a milligram. There is no direct evidence with respect to man which conclusively demonstrates that uric acid formed in the body undergoes chemical change before excretion, and it has been suggested that no such destruction occurs. Evidence pointing toward uricolysis is indirect inasmuch as the theoretical amount of uric acid resulting from ingested nucleins is not recoverable in the urine. The chemical possibilities other than simple oxidation which might explain uric acid destruction in the human organism do not concern us at present, further than to note regarding them that none is demonstrated.

It is an old idea that abnormalities in purin physiology are explicable as a simple retardation of normal processes—"delayed metabolism." Later this conception became more concrete in fixing the blame on the oxidative functions in general (Bouchard<sup>1</sup>). When it became evident that the respiratory exchange might be quite normal even with perverted purin katabolism (Magnus-Levy<sup>2</sup>), the hypothesis of diminished oxidation was narrowed down to specific cellular processes (Ebstein<sup>3</sup>), which it was postulated might conceivably suffer without appreciably affecting

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<sup>1</sup> Manuscript submitted for publication Aug. 24, 1912.

<sup>2</sup> Bouchard: *Les maladies par valetissement de la nutrition* 1890.

<sup>3</sup> Magnus-Levy: *Ueber Gicht* *Ztschr f klin Med* 1899 xxxvi 177.

<sup>4</sup> Ebstein: *Vorlesungen uelluläre Stoffwechselkrankheiten*, 1902.

the sum of the oxygen exchange To those who leaned strongly to the idea that oxidation, in some way or other, must be accounted the important factor in perverted purin metabolism the observation of Munzer was grist to the mill He noted an increased uric acid excretion following poisoning with carbon monoxid and more recently Paton has recorded astonishingly high figures for uric acid excretion in coal-gas poisoning

Because of the theoretical importance of these observations the subject of diminished oxidation in its relation to uric acid excretion was investigated The question is reduced to its simplest terms in the dog, where allantoin, a direct oxidation product of uric acid, is excreted in the urine in considerable amounts Naturally if this allantoin is a derivative of uric acid and is dependent on some oxidizing enzyme for its presence, then an interference with the oxidizing process might increase the uric acid output

Interference with the absorption of oxygen by the body can arise in two ways—(1) By effecting chemical change in the hemoglobin that prevents it from combining with oxygen and fulfilling its carrying function Carbon monoxid poisoning induces this result<sup>4</sup> (2) By decreasing the oxidative power of the cells themselves so that while the oxygen supply may be sufficient the tissues are not capable of utilizing this oxygen Cyanid is the best example of poisons that reduce cellular oxidation<sup>5</sup>

#### AUTHORS' EXPERIMENTS

Our experiments were conducted as follows The dogs were fed on a uniform weighed diet of hashed meat, cracker meal, lard and water After a suitable fore-period the animals were given varying amounts of potassium cyanid hypodermatically Three doses were given daily—at 10 a m and at 4 and 10 p m The doses varied according to the resistance of the animal and were between 10 and 14 mg per kilo body weight The cyanid in all cases was forced to what seemed the maximum tolerance A short period of vomiting was followed in some cases by convulsions, more commonly by a stuporous state Feedings were so arranged that no loss of food resulted from the vomiting following the injection of the cyanid

The results of the experiments with dogs are shown in Table 1

It is possible that uric acid may undergo some destructive change in the human body other than a simple oxidation to allantoin The observations of Paton<sup>7</sup> and Munzer<sup>8</sup> suggest that oxidation is an important step

4 Haldane *Jour Physiol* 1896 *xxiii*, 201 and 430

5 Marthen *Arch f path Anat u Physiol*, 1894, *cxviii*, 535

6 Geppert *Ueber des Wesen der Blausaurevergiftung* Berlin, 1889

7 Paton and Paton *Jour Physiol* 1901, *xxvi*, 166

8 Münzer and Palma *Zeitschr f Heilkunde*, 1896, *xx*, 185

in such a transformation Cases of illuminating gas poisoning that were brought into the New York Hospital were utilized to test this hypothesis A careful selection was made among the cases presented for study since we had no means of knowing at once for what periods the individual had been exposed to gas When the "gas case" was brought into the

TABLE 1 —EFFECT OF CYANIDE ON DOGS  
URINARY NITROGEN  
DOG I

Date 1911	Total Nitrogen, Grams	Uric Acid Nitrogen, Grams	Purin Base Nitrogen, Grams	
March 25, 26	5 01	0168	0196	
March 27, 28	5 17	0182	0210	
March 29, 30	5 13	0187	0210	
March 31 and April 1	4 65	0165	0154	KCN—25 mg T I D
DOG II				
May 17, 18	6 41	0185	0174	
May 19, 20	6 45	0193	0178	
May 21, 22	6 04	0182	0169	KCN—35 mg T I D
May 23, 24	6 29	0203	0158	KCN—40 mg T I D.

TABLE 2 —STUDIES OF URINE IN CASES OF GAS POISONING  
URINARY NITROGEN

Case	Volume Urine, c c	Total Nitrogen, Grams	Ammonia Nitrogen, Grams	Uric acid, Grams
I, 2d 24 h	770	15 22	98	
3d 24 h	610	14 56	1 13	89
II	1710	26 18	1 05	42
III	730	15 67	56	1 46
				86

URINARY SULPHUR

Case	Total Sulphur SO <sub>4</sub> Grams	Total Sulphates SO <sub>4</sub> Grams	Neutral Sulphur SO <sub>4</sub> Grams	Neutral Sulphur Per cent of Total S
I, 2d 24 h	2 70	2 20	50	18
II	5 62	5 15	47	8
III	2 69	2 57	12	4

reception ward from the ambulance the patient was at once catheterized and the urine used for routine tests After this the man was catheterized every six hours and the urine saved If he remained unconscious for twenty-four hours the total urine for that period was used for study If consciousness returned before the full day elapsed the collection was discontinued and study of the case abandoned In this way only such

cases were utilized as had been exposed to gas for some time. Certain unavoidable sources of possible error exist in the employment of these cases. We have no knowledge of the food taken before narcosis. Also all patients were subjected to phlebotomy as a therapeutic measure, but since this is a common factor it is not a serious obstacle in the investigation.

The results of the analyses of the urines are recorded in Table 2. In the first place it is to be noted that the uric acid excretion while high, is not without the bounds of normal for the conditions of this experiment. Carbon monoxide poisoning causes a marked stimulation of katabolic processes, the high nitrogen excretion represents one phase and the uric acid another. No such amounts of uric acid were excreted as were recorded by Paton and one is not justified in ascribing the rather high excretion found to diminished oxidation primarily, since it may be wholly accounted for by other factors. A most surprising fact is that only one of these cases (Case 1) presents tangible evidence of cellular suboxidation. In this case the amount of unoxidized (neutral) sulphur is such a large proportion of the total that diminished oxidation is probably the explanation. This case was apparently profoundly poisoned, judging from the period of coma. In the other cases no such condition was found, yet the uric acid excretion was even greater in some of them.

It is shown by results of analyses here presented that retardations of the oxidizing processes, either by deprivation of oxygen or by interference with cellular functions, were not followed by increased uric acid excretion. It appears improbable, therefore, that uric acid destruction in the body is a simple oxidizing process.

# THE SCAPHOID SCAPULA A NORMAL VARIATION IN MAN \*

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Dr Graves<sup>1</sup> has recently called attention to a type of scapula which he designates as "scaphoid." The character of the vertebral border determines whether a scapula is scaphoid or not. Our best known anatomical text-books<sup>2</sup> describe the vertebral border as "arched," "of curved or somewhat irregular outline" and "nearly vertical from the lower angle to the triangular smooth place on the dorsum opposite the spine." Morris<sup>3</sup> does not mention the curve of the vertebral border, but agrees with the other authors in figuring the bone with a vertebral border gently curved toward the spinal column. Thomas Dwight,<sup>4</sup> in speaking of the variations of the vertebral border, states

The most common form of the scapula presents a line slightly curved at the lower part and then straight as far as the root of the spine, from which point it inclines slightly forward till it ends at the upper angle. The forward inclination of the upper part, though varying in degree is, so far as I know, constant, but the rest of the line varies much. Sometimes it is almost straight, sometimes the whole border of the bone is convex, sometimes the border below the spine is concave.

These scapulae with vertebral borders concave below the spine Graves designates as "scaphoid." He finds them differing from the convex type of scapula, first in having a scapular index of 2.3, less than that of the average type, second, in having vertebral borders more nearly parallel to the long scapular axis, third, in having a spine, as a rule, more nearly at right angles to the long scapular axis, fourth, in having poorly marked anterior and posterior lips, and intermediate surface of the vertebral border, and fifth, in possessing tuberosities varying in size and number, frequently found along the vertebral border, which he calls "border buds."

As normal variations they are of passing interest, but considered as 'A Frequent Anomaly in Development of Hereditary, Clinical and Anatomical Significance,' they at once demand attention.

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\*From the Hearst Anatomical Laboratory of the University of California

1 Graves. The Scaphoid Scapula. A Frequent Anomaly in Development of Hereditary, Clinical and Anatomical Significance. Med Rec, New York May 21, 1910

2 Gray. Anatomy, Cunningham. Text Book of Anatomy. Piersol. Human Anatomy

3 Morris. Human Anatomy

4 Dwight. The Range of Variation of the Human Shoulder Blade. Am Nat 1887




Among 198 dry bones Dr Graves found  
 121 or 61 per cent convex or "normal,"  
 51 or 26 per cent straight,  
 26 or 13 per cent concave or scaphoid  
 Among 72 dry bones examined here  
 34 or 47 per cent were convex,  
 19 or 26 per cent straight,  
 19 or 26 per cent concave or scaphoid

From this we see that the scaphoid scapula is of frequent occurrence

The claim made for its hereditary and clinical significance may be judged from the title to Dr Graves's article, "The Scaphoid Scapula Syndrome Its Connection with Syphilis in the Ascendants"

TABLE 1—RESULTS OF MEASUREMENTS OF SCAPULAE OF MEN

	—Normal—			—Scaphoid—			
	No Obs	No Cases	Result	No Obs	No Cases	Result	
Wing like scapulae, both	134	99	74 0	119	80	67 0	Per cent
Prom acromioclavicular artic	134	88	65 0	119	72	60 0	Per cent
Clavicles — or  *	134	54	40 0	119	58	48 0	Per cent
Abnormal chests	129	41	31 8	109	50	46 0	Per cent
Spinal curves	128	45	34 0	109	38	35 0	Per cent
Palpable glands	129	15	11 0	109	9	8 0	Per cent
Adenoids operated	129	8	6 2	109	3	2 7	Per cent
Tonsils operated	129	14	10 9	109	14	12 0	Per cent
Tonsils enlarged	129	19	14 8	109	19	17 0	Per cent
Abnormal hearts	129	6	4 7	108	3	2 7	Per cent
Abnormal lungs	129	0	0 0	108	1	9	Per cent
Blood-pressure (standing)	120		114 6	108		120 5	mm Hg
Blood pressure (sitting)	118		120 3	108		121 6	mm Hg
Average age	129		20 3	108		19 8	Years
Average weight	98		62 3	88		64 1	kilos
Average height	98		1715 0	91		1747 3	Centims
Average lung capacity	95		4 15	91		4 23	Liters
Lung cap'y less than 2 5 L							Per cent
General development, excellent	129	21	16 0	108	19	17 6	Per cent
General development, good							Per cent
General development, average	129	88	68 0	108	73	67 6	Per cent
General development, fair							Per cent
General development poor	129	20	16 0	108	16	14 8	Per cent
Parents foreign	258	76	29 0	216	65	30 0	Per cent
Parents dead	258	32	12 4	216	20	9 0	Per cent
No children per family	129	511	3 9	108	414	3 8	Per fam
Death rate	129	36	27	108	36	22	Per fam

\*Horizontal or elevated at sternum

Anatomically individuals with scaphoid scapulae are said to differ from average individuals in having longer necks, clavicles more nearly in a horizontal line more prominent acromioclavicular articulations and more prominent "wing-like" inferior angles to their shoulder blades

If scaphoid scapulae are due in any way to syphilis in the ascendants, we would expect to find in individuals having scapulae of this type other evidences of "blight" among which Graves mentions deviating characteristics of the whole individual, the presence of arteriosclerosis at unusually early periods of life, disharmony in physical and mental devel-

5 Graves The Scaphoid Scapula Syndrome Its Connection with Syphilis in the Ascendants Inter-state Med Jour, 1911, VIII, No 1

opment, abnormal degree of lymph-node palpability, relative frequency of adenoids, frequent catarrhal affections developing early in infancy and persisting for years, and nocturnal incontinence

In order to get an idea of the occurrence of the scaphoid scapula and to work out its syndrome from a large number of seemingly average individuals, measurements of the shoulder blades of incoming students of the University of California were made in August, 1912. The relative heights of the two shoulders, the length of the neck, the angle made by the clavicles, the prominence of the acromio-clavicular articulation, and the prominence of the inferior angle of the scapula were noted and recorded.

On entrance to the university all students are given a rigid medical and physical examination. As soon as they were dismissed by the medical examiner they presented themselves for the scapular measurements. The subject stood erect and quiet for a few moments. The vertebral borders of the scapulae were palpated with the index finger and carefully outlined with a blue wax pencil. The prominent bony part of the dorso-lateral extremity of the acromion process was marked and by pressing the full length of the index finger against the caudal border of the crest of the spine the direction of the spine was determined and marked in blue pencil.

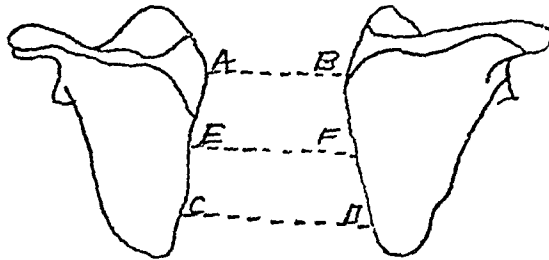


Fig 1—Showing method of determination of variety of scapula

To be sure that the scapulae had not changed in position and that the lines and points were correctly marked, all of the lines of both scapulae were palpated a second time.

The distance between the vertebral borders of the scapulae at the bases of the spines was measured and recorded as distance, *AB* (Fig 1). About  $1\frac{1}{2}$  inches from the inferior angle, a second measurement of distance between the vertebral borders was taken and recorded as *CD*. Half-way between *AB* and *CD*, a third measurement, *EF*, was made.

If the average length of *AB* and *CD* ( $\frac{AB+CD}{2}$ ), is greater than *EF*, the scapulae are convex toward each other. If the average of *AB* and *CD* is equal to *EF*, the vertebral borders are straight, and if the average is less than *EF*, the scapulae are concave toward one another or scaphoid.

In most cases little difficulty was encountered in palpating the points and lines desired, but among the women one swimmer, one violinist, a few obese individuals and several others, offering difficulties of measurement were allowed to pass unrecorded.

In order to select groups having greatest concavity of scapular border, only those having  $EF$  greater than the average of  $AB$  and  $CD$  by more than 1 cm were considered typically scaphoid, and all having vertebral borders in any degree convex toward each other were considered "normal"

In all, 1,067 individuals were measured with the following results

	— Men —		— Women —		— Total —	
	No	Per cent	No	Per cent	No	Per cent
"Normal"	134	21	150	36	286	27 0
Straight	120	19	47	11	167	15 8
Scaphoid by less than 5 cm	104	16	102	24	206	19 5
Scaphoid by from 5 to 1 cm	164	26	76	18	240	22 6
Scaphoid by over 1 cm	117	18	43	10	160	15 1

In order to determine if the scaphoid individuals, as a class, show evidences of "blight," the 134 "normal" men have been contrasted with the 117 decidedly scaphoid men, and the 150 "normal" women with the 43 decidedly scaphoid women

The following tables give the results of the measurements together with other data bearing on the problem. Weights, heights and lung capacities were obtained from the gymnasium records, and the other items from the records of the medical examiners

Chests were recorded as normal, flat, funnel or pigeon-shaped. All of those not recorded as normal were here classed as abnormal. Spinal curves were recorded as normal, lordosis, scoliosis and kyphosis. All other than normal were grouped as abnormal even though the abnormality was marked (slight). Palpable inguinal, axillary and cervical glands were recorded. Tonsil and adenoid observations were made by a specialist. Blood-pressure was measured by a Mercer apparatus accurate to 5.00 millimeters. Heart action was recorded as regular, irregular or intermittent. Where functional disorders were present note was made of the fact. All not marked regular were here classed as abnormal. Lungs were marked negative or special, and note was made of the abnormal respiratory sounds. Under general development such factors as stature, nutrition and general muscular tone, were considered.

The comparative figures do not show that the scaphoid scapula is especially associated with blight or disharmonies. Among both the men and women the average age for entering college is lower for scaphoid than for "normal" individuals which argues well for mental development. Average weights and heights of the two classes are hardly sufficiently different to be worthy of note. The "normal" women average a little heavier and the scaphoid a little taller, while the scaphoid men are both heavier and taller. Among the women there is slightly less lymph-node, tonsil and adenoid enlargement in those of the scaphoid group, whereas among the men the scaphoid group show less lymph-node and adenoid difficulty but a higher percentage of tonsil operation and tonsil enlargement.

The blood-pressure comparisons are of especial importance on account of the fact that the arterial changes shown by those having scaphoid scapulae lead Graves to suspect syphilis as one cause of the imperfect development of the scapula

Among the women the average blood-pressures of the normal and scaphoid groups are identical within the limit of error of the apparatus. Among the men those with scaphoid scapulae show a slightly higher blood-pressure, both when standing and when reclining.

TABLE 2—RESULTS OF MEASUREMENTS OF SCAPULAE, ETC., OF WOMEN

	—Normal—			—Scaphoid—			
	No Obs	No Cases	Result	No Obs	No Cases	Result	
Wing like scapulae, both	136	41	30 0	38	14	37 0	Per cent
Wing-like scapula, one	136	27	19 8	38	8	21 0	Per cent
Prom acrom-clav artic	136	72	52 9	38	17	44 7	Per cent
Clavicles — or $\diagup \diagdown$ <sup>4</sup>	136	45	33 0	38	13	34 2	Per cent
Abnormal chests	136	42	30 8	38	14	36 8	Per cent
Spinal curves	136	18	13 2	38	4	10 5	Per cent
Palpable glands	136	24	17 6	38	6	15 8	Per cent
Adenoids operated	136	11	8 0	38	2	5 2	Per cent
Tonsils operated	136	10	7 3	38	1	2 6	Per cent
Tonsils enlarged	136	10	7 3	38	2	5 2	Per cent
Abnormal hearts	136	12	8 8	38	4	10 5	Per cent
Abnormal lungs	136	6	4 4	38	2	5 2	Per cent
Blood-pressure (standing)	136		120 6	38		120 5	mm Hg
Blood-pressure (sitting)	136		116 0	37		116 8	mm Hg
Average age	118		21 8	32		20 2	Years
Average weight	83		53 6	15		52 7	Kilos
Average height	86		161 7 0	15		1620 0	Centim
Average lung capacity	85		2 53	15		2 34	Liters
Lung cap'ty less than 2 5 L	85	30	35 0	15	5	33 0	Per cent
General development, excellent	136	9	6 6	38	0	0 0	Per cent
General development, good	136	34	25 0	38	6	15 8	Per cent
General development, average	136	71	52 2	38	16	42 1	Per cent
General development, fair	136	19	14 0	38	15	39 5	Per cent
General development, poor	136	5	3 7	38	0	0 0	Per cent
Parents, foreign	272	67	24 6	76	12	15 7	Per cent
Parents, dead	272	32	11 7	76	10	13 2	Per cent
No children per family	136	557	4 10	36	141	3 91	Per fam
Death rate	136	56	41	36	24	66	Per fam

<sup>4</sup>Horizontal or elevated at sternum

The variations throughout the tables are quite such as one might expect to find in comparing two groups of equal numbers selected at random.

So far we are led to conclude that among average individuals between the ages of 16 and 25 the scaphoid type of scapula is of frequent occurrence, but of no clinical significance.

In order to contrast a group of deviates with the student class already studied, 442 inmates of the State Home for the Feeble-Minded at Sonoma, Cal., were examined.

It was quite impossible to get them in good attitudes and keep them quiet so as to outline the vertebral borders of the scapulae and measure them, so palpation had to be depended on.

With the entire length of the index finger of one hand pressed against the caudal edge of the spine of the scapula and directed toward the vertebral border the base of the spine was located. The index finger of the other hand was placed on the vertebral border at this place and the other three fingers spread out along the caudal part of the vertebral border. By their position and by moving them up and down along the vertebral border its character could quite easily be determined, unless it was on the border line between convex and straight or concave and straight. In many

TABLE 3—TOTALS OF TABLES 1 AND 2

	—Normal—			—Scaphoid—			
	No Obs	No Cases	Result	No Obs	No Cases	Result	
Wing-like Scapulae	270	140	51.8	157	94	60.0	Per cent
Prom acrom-clav artic	270	160	59.0	157	89	56.6	Per cent
Clavicles — or $\wedge$ *	270	99	36.6	157	71	45.2	Per cent
Abnormal chests	265	83	31.3	147	64	43.5	Per cent
Spinal curves	264	63	24.0	147	42	28.6	Per cent
Palpable glands	265	39	14.7	147	15	10.2	Per cent
Adenoids operated	265	19	7.1	147	5	3.4	Per cent
Tonsils operated	265	24	9.0	147	15	10.2	Per cent
Tonsils enlarged	265	29	10.9	147	21	14.3	Per cent
Abnormal hearts	265	18	6.8	146	7	4.8	Per cent
Abnormal lungs	265	6	2.2	146	3	2.0	Per cent
Blood pressure (standing)	256		117.6	146		120.5	mm Hg
Blood pressure (sitting)	254		118.15	145		119.2	mm Hg
Average age	247		21.05	140		20.0	Years
Average weight	181		58.45	103		58.4	Kilos
Average height	184		166.6	106		168.3	Centims
Average lung capacity	180		3.34	106		3.28	Liters
Lung cap'ty less than 2.5 L	85	30	35.0	15	5	33.0	Per cent
General development, excellent	265	30	11.3	146	19	13.0	Per cent
General development, good	136	34	24.0	38	6	15.8	Per cent
General development, average	265	159	60.0	146	89	60.6	Per cent
General development, fair	136	19	14.0	38	15	39.0	Per cent
General development, poor	265	25	9.4	146	16	10.9	Per cent
Parents foreign	530	143	27.0	292	77	26.0	Per cent
Parents dead	530	64	12.0	292	30	10.2	Per cent
No children per family	265	1068	4.03	144	555	3.85	Per fam
Death rate	265	92	34	144	60	41	Per fam

\*Horizontal or elevated at sternum

such cases it was impossible to judge positively of the nature of the border and it was recorded as questionable or straight. For this reason the figures indicate a lower number of convex and scaphoid scapulae and a higher number of the straight scapulae than if they had been measured.

On account of the impossibility of making measurements on the deviates, exact comparisons cannot be made between them and the student class.

However, the comparisons are suggestive.

	Student Class, Per cent	Deviate Class, Per cent
Convex vertebral borders	27	22
Straight vertebral borders	15 (straight and questionable)	52
Concave vertebral borders	57	26

Had the student class been palpated instead of measured many of those here classed as normal and apparently scaphoid, would have been put with the questionable or straight

The Wassermann test for syphilis has been made by Dr Linforth on practically all of the women of the Sonoma State Home. Of the 304 whose scapulae were measured, eight gave a positive test. Of these none was under 16 years of age, so that in no case could we safely assume that the disease was congenital. However, among the eight, three had convex scapulae, three straight or questionable scapulae and two scaphoid scapulae.

Since among over 1,000 college students those with scaphoid scapulae show no "blight," and since "normal" scapulae are almost as frequent among deviates as among students, and scaphoid scapulae as frequent among students as among the feeble-minded, there seems to be little cause to consider it an anomaly or to hunt for an explanation for the condition in the history of the individual or his ascendants, and we must, with Thomas Dwight, consider as a normal variation scapulae in which "the border below the spine is concave."

TABLE 4 —TURNER'S FIGURES ON SCAPULAR AND INFRASPINOUS INDICES OF VARIOUS RACES

Race	No of Scapulae	Scapular Index	Infraspinous Index
Lapps	8	62.0	85.9
Esquimaux	8	61.0	81.3
Tasmanians	6	60.3	81.4
Australians	28	64.9	88.5
Bushmen	10	66.2	89.7
Polynesians	32	66.6	89.4
Peruvians	46	66.5	89.6
Fuegeans	9	65.0	
Europeans	462	65.3	87.8
Negroes	100	69.7	98.5
Andamanese	27	70.2	97.3
Melanesians	26	69.8	93.8
Malayans	10	68.9	93.8

Much attention was directed to the scapula by the paper read by Broca before *La Société d'Anthropologie* in 1878, in which he defined scapulae and infraspinous indices, and proposed them as methods of determination of race. He found Negroes, Andamanese and Australians to have high indices, which means broad scapulae, and speaks of them as "consequently of a lower type," having already pointed out the fact that in all orders of animals, except bats, the scapular index is greater than in man.

During the following year many measurements of scapulae were undertaken. Thomas Dwight, of Harvard, collected what data he could from others, and adding to them his own findings, largely obtained from bones of American Indians, published an article in the *July American Naturalist*, in 1887, on "Variations of the Human Scapula," in which he concluded that the Kentucky Mound Builders had decidedly higher indices, or, in other words, broader scapulae, than the Caucasians.

Dorsey, on the contrary, found the West Coast Indians to have a mean scapular and infraspinous index lower than any yet recorded for any race except Esquimaux, Hottentots and Tasmanians

Sir William Turner, in his "Report on the Bones of the Human Skeleton," gives the figures shown in Table 4

In conclusion to his comparison of the scapulae he says

Should there be anything in the habits of one race of men which might require a particular group of scapular muscles to be used and developed to an extent far greater than in another race, then it is not unlikely that the area of attachment of these muscles in that race would be widened and lengthened to an extent greater than in the case of those races in which the same group is not similarly exercised, and the proportion of those parts of the scapula to the rest of the bone would in so far be modified. The arboreal habits of the ape require that it should use its upper limbs for purposes of climbing and for swinging itself from one branch of a tree to another, so that the muscles engaged in the elevation of the upper limb require to be powerful, which would account for the greater development of the supraspinatus muscles and fossa, and would probably lead also to the greater obliquity of the scapular spine than in the case of man. In a similar manner one would expect to find in those races of men, as the Australians, who climb trees in quest of food, or those natives in the interior of New Guinea, whose houses are built in the upper branches of lofty trees, a commensurate development of the elevatory muscles of the upper limb and of their respective areas of attachment. But in connection with this development, the additional area might be obtained, either by an addition to the length or breadth of the surface, or perhaps both to the length and breadth.

Considering the subject from an evolutionary point of view and accepting the underlying idea of Sir William Turner's quotation, we may consider that as a primitive race we inherit broad scapulae with convex vertebral borders and those races making much use of their shoulder muscles have best preserved such scapulae, that among civilized races where the arms are comparatively little used decrease in size has followed decrease in use. The decrease may be either in length or breadth or both and may account for the scaphoid scapula.

Since evidence for considering the scaphoid scapula as an anomaly of development is lacking, and since it is possible that man's upright position might lead to such a variation from the animal type, it seems logical from the biological standpoint, as well as from the clinical, to consider the scaphoid scapula as a normal variation.

In addition to the references numbered in the text the following are given

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# ERYTHREMIA, OR POLYCYTHEMIA WITH CHRONIC CYANOSIS AND SPLENOMEGALY

REPORT OF TWO CASES WITH A SUMMARY OF 179 CASES  
REPORTED TO DATE<sup>1</sup>

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Renewed interest has recently been shown in that primary form of polycythemia with chronic cyanosis and splenomegaly which was first brought to the attention of the profession in 1892 by H. Vaquez,<sup>1</sup> and which has been well termed "erythremia" in contra-distinction to "erythrocytosis" or secondary polycythemia.

Erythremia was long considered a rare condition and as late as 1907 Mackey,<sup>2</sup> in a most excellent thesis, was able to cite but about forty cases. During the past few years, however, the increasing number of patients reported from various sources indicates that the malady is not by any means as uncommon as was at first supposed. Indeed, Stachelin,<sup>3</sup> in 1911, reported eleven cases of polycythemia which came under his observation in a single year, of which at least six appear to have been of the Vaquez type.

As the result of a recent careful search through medical literature, I have succeeded in collecting reports on 179 cases of so-called polycythemia, of which 149 cases appear to be unquestionable instances of erythremia, the other thirty cases being open to doubt as to their true classification.

The two cases which have come under my observation and which aroused my interest in the condition are as follows:

## CASE REPORTS

CASE 1.—B. W., male, married, white, aged 52, a native of Russia, grocer, was admitted to the service of Dr. H. A. Hare in the Jefferson Medical College Hospital, May 19, 1911. Family history is unimportant, no history of malignant or tuberculous disease.

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\*Manuscript submitted for publication July 15, 1912.

<sup>1</sup>Ten additional cases have been collected since this paper was prepared for publication and too late to permit of their inclusion under the proper classification in the summary at the end of this article. These ten cases have been shown separately at the end of the summary thus making a total of 189 cases in all.

1 Vaquez, H. *Compt rend Soc de biol*, 1892, series 9, p. 384, also *Bull mcd Paris* 1892, vi, 849.

2 Mackey. *Birmingham Med Rev*, 1907, N. S., viii, 113 and 177.

3 Stachelin. *Beil klin Wehnschr*, 1911, xlviii, 101.



Patient had measles in childhood. At the age of 20 he had an attack of pleurisy, was seriously ill and had a cough for some time subsequent but afterward became perfectly well.

On Feb 5, 1906, he was operated on at the German Hospital by Dr John B Deaver for a prostatic abscess, which was opened through the perineum and drained with an uneventful recovery. Subsequent to this operation he noticed that his color was changing and he became blue. Is said (by himself) to have had a puncture in the right kidney region and that pus was found, this operation being within a comparatively short time after the other. The physician who did this puncture has since died.

At about this time he went to the Pennsylvania Hospital on account of failing vision, dizziness, etc. His symptoms then were the same as at present, namely, headache, vertigo, hazy vision and a feeling as though his head was stuffed with blood.

From that time his general health was good with the exception of attacks of "asthma," cough and shortness of breath, up to May, 1910, when he began to have attacks of headache, confined to the right side of his head, and accompanied by dizziness and shortness of breath. Following these attacks his hands, face, lips and nose became dusky, the duskiess lasting from two to twenty-four hours.

Beginning in the Autumn of 1910 he had frequent attacks of indigestion which seemed to precede the attacks of cyanosis and headache.

Since January, 1911, he has had considerable difficulty with his eyes, stating that he has scarcely been able to read a newspaper and that he has had a continual haze over his eyes and that stooping or suddenly turning his head brought on dizziness and cyanosis. He also complained of a lump in the throat on swallowing.

*Examination*—Patient is a well nourished and well developed adult. Skin is dry and warm. His face, and especially his nose, lips, cheeks and ears are of a bluish-red color. The hands, wrists and arms to elbows are bluish red. Dorsum of feet present nothing abnormal but the soles both are bluish-red and somewhat edematous. The tongue is red and coated with grayish fur. The pharynx is purplish red.

Fingers are clubbed with slightly curved nails.

The examination of the abdomen proved negative, the liver not being enlarged and the spleen showing no enlargement except on one occasion during an exacerbation, when it was very slightly enlarged.

The chest is symmetrical, expansion equal and full, hyperresonant throughout, a few moist râles heard over both bases. Respiration 22.

Heart sounds rhythmical, distant at apex, maximum intensity in epigastrium where the sounds are clear. Pulse 92. Blood pressure, systolic 120, diastolic 86.

None of the superficial lymph-nodes palpable.

Genitals negative. A scar observed two inches below last rib on right side.

Wassermann test proved negative.

X-ray examination reveals many enlarged mediastinal glands.

Eyes. Pupils dilated, equal and react normally. Double optic neuritis with four diopters of swelling in each eye and hemorrhages into the retina. Vision about one half normal with glasses. Fields concentrically contracted about one half. (See subsequent reports.)

Temperature 98.6

Urine. Slightly turbid, amber, 1019, acid, faint trace of albumin, no sugar, crystals, blood or casts, a few urates, epithelial cells and leukocytes. Urea 2 per cent. Practically the same on a number of subsequent examinations. Quantity during first week in hospital averaged 500 cc for twenty four hours, next two weeks averaged 1,200 cc, dropping to an average of 700 cc during rest of stay. During second short stay in hospital the average was 500 cc.

*Course*—Patient's temperature on admission was normal and during his stay ranged between 97 and 99 F with one rise of short duration to 100.6 and one drop to 96.4

From May 20, 1911, the day after admission, to June 14, 1911, date of discharge, his weight dropped from 129.5 to 120 pounds

Pulse rather irregular, ranging between 80 and 100 with one rise to 110 and one drop to 74. His respiration was usually about 22 although occasionally as high as 30. Bowels moved once or twice daily with, occasionally, laxatives.

His cyanosis continued throughout his entire stay in the hospital. Until May 20 he was free from headaches and dizziness but on that date had several attacks of dizziness, lasting a few minutes each, and also a slight right-sided headache.

On May 21 he had two brief attacks of dizziness due to suddenly turning the head to the side and stooping. Also complained at this time of drawing sensation in calf of left leg.

Date	Erythrocytes	Hgb	C I	Leukocytes	Polymorpho-nuclears, %	Lymphocytes per cent	Hyaline per cent	Remarks
1911								
5-12	7,810,000	135	86	8,200				From finger
5-13	8,060,000	138	86	8,800	54	20	15	From toe, also 9 per cent eosinophils and 2 per cent degenerated eosinophils
5-22	8,660,000	140	81	8,000	57	27	8	Eosinophils 2 per cent and neutrophilic myelocytes 6 per cent
6-9	7,900,000	129	81	7,400				Before bleeding
6-9	6,530,000	127	97	6,880				After bleeding
6-9	6,800,000	112	82	7,200	80	15	6	No parasites. Morphologic characteristics correspond to normal red cells
11-9	6,470,000	125	97	10,200	74	15	7	Eosinophils 2 per cent, degenerated 2 per cent
11-25	6,130,000	138	113	9,200				Before bleeding
11-25	5,200,000	96	92	7,500				After bleeding

On May 23 again complained of being dizzy at irregular intervals.

On June 9, 16 ounces of blood removed from right median basilic vein. Was slightly improved on June 12 and was discharged on June 14.

Patient then felt very well until about the last of September, 1911, when old symptoms returned, and on November 8 he was readmitted, his condition in general being about the same as in June. The extremities at this time showed a slight pretibial edema. Eye examination revealed a swelling of two diopters in each eye. Vision 20/30 with glasses. Fields contracted about one-half as before. No hemorrhages. Every evidence of a subsiding inflammation with probably a secondary atrophy obscured by the inflammatory changes.

The patient received no medication at this time except laxatives and was up and around the ward the second day, apparently very comfortable and was discharged on November 13.

November 25, 1911, patient returned to ward for venesection to relieve symptoms of dizziness, his condition being about the same as before, 16 ounces of

blood being withdrawn from superficial vein of right elbow. No change was noted in his condition immediately following venesection but he felt better on the following day, his color being less dusky, and he was discharged with instructions to report to the out-patient department.

For some time thereafter he reported regularly at the out-patient department and was bled four times with temporary relief. An *x* ray examination of the chest at this time showed the heart to be apparently of normal size, rather horizontally placed. There seemed to be multiple adhesions between the pericardium and the diaphragm, also marked thickening of the peribronchial glands.

No parasites or organisms of any kind were found in the blood at any time.

In January, 1912, the patient spent several weeks in the German Hospital, where, in addition to other treatment, he was subjected to treatment by the *x* ray over the long bones. His condition at this time was about the same as before and he was not permanently benefited by treatment.

Recently he has been a patient at the Pennsylvania Hospital complaining of an exacerbation of symptoms. Dr. William T. Shoemaker, who examined the patient on both of the occasions when he was in the Pennsylvania Hospital, and who has kindly given permission to include the results of his observation of the eye grounds, states: "Although of course, interesting in many ways, special interest from an ophthalmic standpoint lies in the *violent* changes which are shown in the optic nerve, retina and blood vessels. These changes are those of *typical inflammatory choked disk*, identical, it would seem, with those frequently seen with intracranial disturbance."

The patient recently advised me that for some time he has been subject to periodic hemorrhages from the bowel, occurring on an average of once in six weeks and followed by some temporary relief.

Despite all treatment his general condition at present is about the same as when first seen.

CASE 2.—Male, aged 43, Russian Jew, vest maker, was admitted to the service of Dr. H. A. Hare in the Jefferson Medical College Hospital April 22, 1912, complaining of severe headache, dyspnea, dizziness and nervousness. His bowels were constipated, appetite poor.

Family history unimportant, so far as he knows no member of his family has suffered in a similar way.

He came to the United States from Russia twenty years ago and since his arrival in this country has worked continuously as a vest maker. For four years prior to leaving Russia he was a soldier.

For fifteen years he has been troubled with "asthma" and cough.

Suffered from hemorrhoids for fifteen years, undergoing an operation ten months ago for relief from same.

Has had more or less headache for six years.

Three months ago had a slight attack of hemoptysis.

Two weeks prior to admission he began to suffer from severe headache, dyspnea, dizziness and nervousness.

Two days prior to admission his wife called his attention to the change in his color. He is somewhat myopic.

Examination.—The patient is a well nourished adult male.

His face is somewhat cyanotic, being markedly so when he lies down. The lips and ears are markedly dusky and the hands slightly so. The tongue is very red and the buccal mucosa and pharynx are bluish-red.

Spleen was not palpable.

Liver dulness was slightly increased.

Lungs. Prolongation of expiration and many rales throughout the chest. Resonance impaired anteriorly at the right apex and slightly impaired posteriorly at both bases. Respiration 32.

Heart. Faint systolic murmur at the mitral area. Muscle tone fairly good. Pulse somewhat rapid on admission (118) falling to 96 the following day.

## WALTER S. LUCAS

Systolic blood-pressure 132

Legs and feet swollen and edematous, pit on pressure

Temperature 99.4 F on admission, 98.4 the following day

Eyes React normally to light and accommodation Pupils equal There is a marked congestion of the conjunctiva and retina

Urine This showed a very faint trace of albumin, no casts

Sputum Negative as to tubercle bacillus

Blood The red cells were 8,430,000, hemoglobin 95 to 120, white cells 8 to 13,400 Polymorphonuclears 70 per cent, small lymphocytes 16 per cent, large lymphocytes 12 per cent, eosinophils 2 per cent, blood platelets four in one

X-Ray—X-ray examination of the thorax revealed marked peribronchovascular thickening, particularly on the left side, and bronchiectasis

Treatment—Under treatment with morphin sulphate, atropin, epinephrin, and opium, purgatives and, finally, elixir iron, quinin and strychnin, patient died in hospital with general condition apparently considerably improved

Six months later Condition unchanged Had several exacerbations and the symptoms were sufficiently severe to require venesection, which gave prompt but only temporary relief

### SYNONYMS

Erythremia, or primary absolute polycythemia, is also known as Vaquez's disease, Osler's disease, polycythemia with chronic cyanosis, myelopathic polycythemia, splenomegalic polycythemia (Weber<sup>4</sup>), congenital polycythemia (Cabot), and erythrocytosis megalosplenica (Senator<sup>5</sup>) The term erythremia, suggested by previous authors,<sup>6</sup> seems especially appropriate, distinguishing the condition as it does from erythrocytosis,<sup>7</sup> or polycythemia rubra of known origin, just as the terms leukemia and leukocytosis distinguish analogous condition in which the white cells are particularly affected

It is probable that cases of erythremia were formerly reported under such headings as "plethora," "venous congestion with cyanosis," and, as Herringham<sup>8</sup> points out, Cuffer and Sollier's two cases<sup>9</sup> of "congestive venous diathesis," reported in 1889, may have been examples of this disease

### HISTORY

In 1892, Prof H. Vaquez,<sup>1</sup> of the Faculté Médecine, Paris, reported a case of peculiar cyanosis with persistent polycythemia, which he regarded as due to congenital heart disease The liver and spleen were enlarged and the red cells and hemoglobin greatly increased On the death of the patient in 1895, Vaquez discovered the absence of organic heart involvement

4 Weber Med Clin Tr, London, 1905, LVIII, 191

5 Senator Ztschr f klin Med, 1906 LX, 357

6 W Turk, Hirschfeld and W Osler

7 This term was suggested by Hirschfeld

8 Herringham Brit Med Jour, May 9, 1908, I, 1096

9 Cuffer and Sollier Rev de Med, Paris, 1889, LXII, 825

In 1899, Rendu and Widal<sup>10</sup> reported the case of a policeman with enlarged spleen, marked cyanosis and polycythemia. At autopsy the heart was found to be normal, but the spleen was tuberculous and contained large caseous areas. The bone marrow contained nucleated red cells pointing to over-activity. Rendu and Widal concluded that the disease was due to primary tuberculosis of the spleen, which conclusion has not, however, been sustained by subsequent investigation.

At about the same time two cases were reported by Cabot,<sup>11</sup> one by Cominotti<sup>12</sup> and one by McKeen.<sup>13</sup>

Erythremia was first referred to as a clinical entity in connection with a case reported by Saundby and Russell,<sup>14</sup> in 1903. It was not, however, until the appearance of Osler's papers,<sup>15</sup> in 1903 and 1904, that the condition was brought prominently before the profession in this country and its existence established.

During the five years which have elapsed since the appearance of Mackey's thesis an increasing number of cases have been reported annually. One hundred and forty-nine apparently unquestionable cases are now on record, which number would undoubtedly be considerably augmented were all the facts known in connection with the thirty additional cases which have been included in the questionable list in the summary at the end of this article.

#### ETIOLOGY

The cause of the disease is unknown. Rendu and Widal<sup>10</sup> attributed it to primary splenic tuberculosis and considered that the diminished function of the organ caused increased erythroblastic activity of the bone marrow.

Collet and Gallavardin,<sup>16</sup> in 1901, reported a case of "massive primary tuberculosis of the spleen," in which the blood-cells were not counted, but in which the general physical features of the blood were similar to cases of erythremia.

Vaquez,<sup>17</sup> in 1899, Turk,<sup>18</sup> in 1902 and Osler,<sup>19</sup> in 1903, stated their belief that the disease was not due to splenic tuberculosis, but that, on

10 Rendu and Widal *Bull Med Soc d hôp*, 1899, III, ser., page 528.

11 Cabot *Boston Med and Surg Jour*, March 15, 1900, cxi, 275, and Dec 7, 1899 cxi, 574.

12 Cominotti *Wien klin Wchnschr*, 1900, LVII, No 39, p 881.

13 McKeen *Boston Med and Surg Jour*, June 20, 1901, cxiv, 610.

14 Saundby and Russell *Lancet*, London, 1902, I 515. *Brit Med Jour*, 1907, I, 1165.

15 Osler *Am Jour Med Sc*, Phila, 1903, N S, cxxvi, 187-201. *Brit Med Jour*, 1904, I, 121.

16 Collet and Gallavardin *Arch de mcd exper et d'anat path*, 1901, LVII, 191.

17 Vaquez "Hyperglobulie et Splenomegalie," *Bull Soc méd d hôp*, Paris, June 16 1899, p 579.

18 Turk *Wien Ges f inn Med*, 1902.

19 Osler *Jour Med Sc Phila*, 1903, N S cxxvi 187-201.

the other hand, it was due to a primary hyperplasia of the erythroblastic bone marrow

According to Weber,<sup>20</sup> objection to the view that the excessive formation of red cells in the bone marrow is the primary condition in erythremia has been urged by Lommel, Bence and others. In several cases of (clinically) splenomegalic polycythemia (erythremia) evidence of local or general blood stasis has been found suggesting that the polycythemia was secondary. Bence states that the polycythemia in the splenomegalic type can be diminished by oxygen inhalation, but Stern and others obtained negative results by this method.

As having a possible bearing on the etiology of the condition, Weber<sup>20</sup> suggests that it may be considered analogous to leukemia, or as a result of a reversion to, or persistence of, fetal and early life conditions in which the bone-marrow is red and still actively engaged in the formation of red cells.

Nervous excitement, mental worry, toxemia originating in the spleen, lungs or alimentary canal, and compensatory reaction towards some hypothetical disturbance in the gas exchanging functions of the blood have all been suggested as possible causes of the disease.<sup>21</sup>

Reckzeh,<sup>22</sup> reporting a case of polycythemia occurring in a male of 24, in which there was progressive compression of the superior vena cava by a malignant tumor of the thymus, was inclined to consider stagnation of the blood, from various causes, as the sole cause of erythremia, but Osler<sup>23</sup> does not consider his reasons or experiments convincing, and Behr<sup>24</sup> says, "The view that the increase of red cells and the general cyanosis are the result of a simple stasis appears rather forced if we consider that, while such cases of acquired stasis are frequent, yet such cases accompanied by polycythemia are extremely rare."

Anders<sup>25</sup> case led him to consider defective venous tone as playing an important rôle in the pathogenesis.

A theory, which has the support of Metchnikoff, assumes that some toxin of a hemolytic nature is manufactured by the enlarged spleen and is absorbed into the circulating blood in minute quantities, not sufficient to cause hemolysis, but sufficient to excite reaction in the blood-forming organs. Belonovsky,<sup>26</sup> by injecting minute doses of hemolytic serum into the blood of anemic individuals succeeded not only in raising the number of red corpuscles, but also the amount of hemoglobin.

20 Weber *Quart Jour Med*, Oxford, January, 1908, 11, 85

21 Allbutt and Rolleston's *System of Medicine*, 1909, v, 831

22 Reckzeh *Ztschr f klin Med*, 1905, lvii, 215

23 Osler *Modern Medicine*, 1908, iv, 678

24 Behr *Klin Monatsbl f Augenh*, 1911, xlix, 672

25 Anders *Am Jour Med Sc*, 1907, N S cxxxiii, 829

26 Belonovsky *Sur l'Influence de l'injection de diverses doses de serum hemolytique sur le nombre des elements du sang*, St Petersburg, 1902

The blood has been examined in several cases for methemoglobin and sulphhemoglobin with negative results

**Age** The disease is comparatively uncommon in early life, only 12 per cent of the patients being under the age of 30, while 64 per cent occurred between the ages of 40 and 60

The two youngest patients were girls, aged 17, one being reported by Chace (Case 58 in summary) and the other by Sandesky (Case 67), and Reissmann (Case 94) and Hann (Case 108) each reported a case occurring in a girl of 18. It is true that Guinon, Rist and Simon (Case 152) reported the case of a girl of 10 years with polycythemia, cyanosis and splenomegaly, but in the case in question there was chronic jaundice and the polycythemia and cyanosis were transitory, it cannot, therefore, be regarded as a case of erythremia

At the other extreme of life is the case of a female of 68 reported by McQuitty (Case 102)

The cases<sup>27</sup> were divided with respect to age as follows

	Per cent
Second decade	4
Third decade	8
Fourth decade	18
Fifth decade	37
Sixth decade	27
Seventh decade	6

**Sex** Sex has no noteworthy bearing, although the proportion of male to female patients is about two to one. In the 140 cases in which the sex is stated, eighty-nine occurred in males and fifty-one in females

**Occupation** Has no particular bearing beyond the probability that an active life was led by the majority of the patients, judging from those cases in which the occupation is stated

**Race** As the nativity is given in but twenty cases, no satisfactory conclusions can be drawn as to the influence of race on the occurrence of erythremia. In the twenty cases in question ten of the patients were Hebrews, three natives of the United States, two each English and German, and one each Irish, Dutch and Polish. Of the remaining 129 cases sixty-six were reported in German publications, thirteen in the United States, seven in Italy, five in France, four in Hungary and one each in the Philippine Islands and Australia

#### SYMPTOMS

Erythremia is characterized by marked, persistent and absolute increase of the red blood corpuscles, marked increase in the viscosity and total volume of the blood, excessive erythroblastic activity of the bone-

<sup>27</sup> All statistics given in this article refer only to the 149 cases in Tables A, B, C and D of summary appended, the thirty doubtful cases in Table E not being taken into account

marrow, and, usually, by characteristic changes in the eye-grounds, cyanosis and enlargement of the spleen

Weber<sup>20</sup> suggests that the sequence of events is probably as follows:

- 1 Increased erythroblastic activity in the bone-marrow
- 2 Increased viscosity of the blood resulting from this polycythemia.
- 3 Dilatation of the small blood-vessels so as to lessen the resistance to the abnormally viscid blood
- 4 Arterial hypertonia as a result of the great strain thrown on the circulatory mechanism

5 Cyanosis when it occurs, is probably due to the inadequacy of the series of compensatory changes which precede it

The physician's advice is usually sought on account of (1) the abnormal color of the skin and mucous membranes (present in 83 per cent of cases), (2) the symptoms of cerebral congestion, such as headaches (present in 31 per cent of cases), and vertigo (34.5 per cent of cases), (3) dyspnea (19.5 per cent of cases), and (4) lassitude and weakness (19.5 per cent of cases)

Twenty-three per cent of the patients complained of hemorrhages, 19 per cent of pain in the left hypochondrium and 14 per cent of loss of flesh

Occasional symptoms were constipation, vomiting, indigestion and palpitation, each in about 10 per cent of the cases, swelling of the limbs, cough, edema and clubbed fingers, each in about 6 per cent of cases, and disturbed menses, tinnitus aurium, anorexia, fulness of head, sweating and diarrhea, each in about 4 per cent

**Cyanosis** In 75 per cent of the cases summarized by me in the tables at the end of this article distinct cyanosis was present, and in about 8 per cent of the cases it is stated that the patient, while not distinctly cyanosed, was "very red," "florid," "face congested," "plethoric," etc., so that in 83 per cent of the cases there was some intensification of the color of the skin

Cyanosis was absent or not reported in 17 per cent of the cases

It was one of the first symptoms in 15 per cent of the patients

The cyanosis may be general, but is usually more marked in the face and hands. The tongue is nearly always a characteristic bluish red color. The patient may be deeply cyanosed, moderately cyanosed, or there may be merely a florid appearance with great dilatation and engorgement of the superficial vessels. The most common condition appears to be a distinct cyanosis of the face, more marked in the nose, ears, cheeks and lips, duskiness or deep redness of the tongue and mucous membranes; and more or less discoloration of the hands. From this it will be observed that the cyanosis is most common in the exposed portions of the body.



Discoloration of the feet was reported in two cases (5 and 124) and of the trunk in two cases (20 and 69)

Exposure to cold and mental excitement seems to intensify the cyanosis, while a warm room may cause the blue color to give place to red. The symptoms seem to subside somewhat in summer (Case 12)

In a number of cases the patient presented a striking appearance. One of Osler's patients (Case 10) was known as "the blue baby." Aldrich and Crummer's patient (Case 47) was called "the red Indian woman." Other authors spoke of the cyanosis as "extreme," "intense," "startling," "remarkable" and "extraordinary."

**Skin, Mucous Membranes, Etc.** Vascular engorgement is usually noted in the buccal and pharyngeal mucous membranes, conjunctivae and the interior of the eye and frequently in the superficial vessels. In 25 per cent of the cases the veins are described as being distended and the conjunctivae was reported injected in 19 per cent.

In 3 per cent of the cases slight pigmentation of the skin is reported. Carbuncle, erythema, bronzing, psoriasis and *tâche cérébrale* were each reported in one case.

Osler drew attention to the fact that a white line could be produced by cutaneous irritation, a sign which some French writers supposed to be connected with functional insufficiency of the suprarenals.

Dermatographia and erythromelalgic symptoms have been reported in a few cases.

**Lungs.** Usually either no mention is made of the lungs or they are reported as being normal. Dyspnea, however, is recorded in 19.5 per cent of the cases, some degree of emphysema in 8 per cent and cough in 6 per cent. Asthmatic attacks were reported in three cases and excessive expectoration in two cases.

**Heart and Circulatory System.** In only a very few cases was the cardiac involvement worthy of consideration. No mention was made of the organ in 28 per cent of the reports, 30 per cent report the heart normal, 27 per cent state that the heart was somewhat enlarged, and 15 per cent call attention to very slight cardiac irregularities. If, then, a normal heart be assumed in the 28 per cent of cases in which the organ is not referred to, 58 per cent of the patients were without demonstrable heart abnormality.

Palpitation was reported in 10 per cent of the cases, tachycardia in four cases and in one case (94) a pulse-rate of 160.

With reference to disturbances in circulation, the feet and legs were blue, swollen and painful in 9 per cent of the cases, edema and clubbing of fingers and toes each occurred in 5 per cent, arteriosclerosis, varicose veins, thrombosis, gangrene, hemorrhoids and incurvated nails each in

3 per cent, phlebitis in two cases, cold extremities in one case    Anemia preceded one case

Hemorrhages    Hemorrhage seems to have been a very prominent symptom, occurring in about one-fourth of all cases, as follows

	Cases
Epistaxis	in 10
Gums swollen and bleeding	in 12
Cerebral hemorrhage	in 3
Hematemesis	in 6
Hemoptysis	in 2
Melena	in 5
Hematuria	in 2
Menorrhagia	in 2
Mucous hemorrhage	in 1
Miscarriage and severe hemorrhage with relief	in 1
Prolonged hemorrhage after extraction of teeth	in 1

Epistaxis was very marked in one case (58)

Blood-Pressure    Unfortunately, the blood-pressure was reported in only about 60 per cent of the cases. In sixty-six reports of cases in which the blood-pressure was taken, twenty-one gave the systolic pressure as below 140, while forty-five reported pressures ranging from 145 to 310, as follows

	Cases
Blood pressure 145 to 170	23
Blood-pressure 180 to 200	13
Blood-pressure 210, 235, 240 and 310, each one case	4
Blood-pressure 220	3
Blood-pressure 200	2

It is interesting to note that in eight cases in which the authors report an absence of splenic enlargement the systolic blood-pressure was comparatively low—110 to 130 in five cases, 140 in one and 150 in two—whereas in twenty cases making no mention of the spleen (from which it may be assumed that the organ was not enlarged) the blood-pressure appears to have been uniformly high, ranging from 150 to 210 in fourteen cases and in six cases (Cases 130, 132, 135, 138, 139 and 142) being reported as from 220 to 310. From this it would appear that, notwithstanding the comparatively low pressure in the eight cases referred to, the blood-pressure is usually above normal in cases showing no splenomegaly (Geisbock's polycythemia hypertonica)

On the other hand, in thirty-eight cases reporting a distinct splenic enlargement, the blood-pressure was below 150 in twenty cases and only exceeded 200 in two cases (82 and 145)

Spleen    Some enlargement of the spleen was present in about three-fourths of the patients. The organ was not mentioned in 18 per cent and was not enlarged in 8 per cent

In the 110 cases in which splenomegaly was reported, forty-six reported marked enlargement, fifty-four slight enlargement as determined

by palpation, seven cases "percussion enlargement" and in three cases enlargement was found at autopsy

Of the forty-six cases in which there was marked splenic enlargement, twenty-one cases reported the spleen as reaching to the level of the umbilicus and nine as reaching to or below the iliac crest

It is worthy of note that in one case (120) an accessory spleen was found on exploratory incision and in another case (81), what was thought to be a supernumerary spleen was palpated by the examiner

**Liver** The liver did not show any increase in size in the majority of the cases, about a third of the patients presented a *slight* enlargement of the liver, but not to the extent seen in the spleen. A tremendous enlargement of the liver was present in one case (90), and a marked enlargement in six other cases

**Gastro-Intestinal System** In about half of the patients there was disturbance of the gastro-intestinal system. Vomiting was present in 12 per cent of the cases, constipation in 11 per cent, indigestion in 9 per cent, diarrhea in 4 per cent, anorexia, jaundice, nausea and thirst each in 3 per cent, and stomatitis, hiccough, eructations and ascites each in one case

**Temperature** The temperature, as a rule, is not affected. Fever was reported in but five cases and subnormal temperature in but three cases

**Generative Organs** There was disturbed menstruation in seven cases, prolapse of the uterus in two cases, atrophy of the uterus in one case and in one case (105) the general condition was worse before commencing of menstruation and after the menopause

**Pain** In over a third of the cases the patient complained of pain in some form, headache being the most constant, occurring in 31 per cent of all cases. Pain in the left hypochondrium was complained of in 19 per cent, in many cases both headache and pain in the left hypochondrium being present. Pain in the chest was present in four cases, pain in the right hypochondrium and tenderness over the bones each in three cases, cramps in the legs in two cases, and neuritis, neuralgia, precordial pain, lumbar pain, pain in the stomach, pain in fingers and toes, shooting pains in the hands, pain between the shoulders and pains in the joints each in one case

**Nervous System** The nervous system appears to have been affected in many cases. The following symptoms have been reported: Tinnitus aurium (in 5 per cent), apprehension, nervousness, excitability, delirium, irritability, hypochondriasis, disturbed mentality, insanity, insomnia, minus knee-jerks, muscular atrophy, numbness, choreiform attacks, epileptiform attacks, muscular twitching, shivering, tremor, paralysis,

hemiplegia, aphasia, disturbed speech, paraphasia, "heat in head," "lump in throat," fainting, loss of consciousness, syncopal sensations without loss of consciousness, etc

**Eyes** The eye condition in cases of erythremia is especially noteworthy and a careful ophthalmoscopic examination should be made

The importance of such an examination does not appear to have been appreciated by most of the authors, the eye being mentioned in only forty-four cases (30 per cent), and an ophthalmoscopic examination having been made in only twenty-six cases (18 per cent)

White, in reporting a case (Case 119), says "Judging from the appearance of the fundus oculi, I should say that the condition would always be easy to recognize"

According to Holloway,<sup>28</sup> on the other hand, the fundus picture in erythremia cannot be distinguished from the changes produced by congenital heart disease with cyanosis, except that, in his opinion, the congenital cases as a group would tend to show more extensive intraocular changes than would cases of erythremia

Behr, in writing on this point, says <sup>24</sup>

It must be of great importance for the conception of the symptom-picture if we can establish the specificity of the disease by some special symptom which is only found in primary erythrocytosis but never in simple chronic stasis without polycythemia. By its establishment in the so called secondary cases we can then remove the principal difference between the idiopathic and symptomatic erythrocytoses. Such a symptom we possess in the characteristic changes in the fundus of the eye

Disturbances of vision were reported in thirteen cases, Hutchinson and Miller's patient (Case 34) becoming quite blind, although nothing was found in the optic disks beyond a slight hyperemia and engorgement

The conjunctiva is usually injected and in those cases in which an ophthalmoscopic examination was made the retinal veins are almost universally reported as being dark colored and dilated and frequently tortuous

Parker and Slocum's patient (Case 78) had blurring of vision and occasional diplopia, the veins of the fundus were markedly tortuous and dilated and the retina edematous and deeper red than normal

The same authors reported a second patient (Case 79) entering the ophthalmologic clinic complaining of severe frontal headache, blurring of vision and diplopia. Examination revealed vision O/D 6/7 5, O/S 6/9, retina hyperemic, veins much engorged, tortuous and dark in color

Hall's patient (Case 86) was carefully examined by Jackson<sup>29</sup> on a number of occasions during a period of two years, the results being set forth in detail in an excellent article accompanied by a plate showing the appearance of the fundus oculi. This patient when first seen

<sup>28</sup> Holloway New York Med Jour, Jan 13, 1912, xcv, 69

<sup>29</sup> Jackson Ophthalmology, Milwaukee, 1907 iv, No 1

Jackson showed an indefinite blurring of vision, epiphora, dilatation of the retinal veins, decreased vision unimproved by any lens, and a slight rotary nystagmus. Later the pupils became unequal and the vision still less and the sinus of the left nerve became markedly larger and distinctly bluish towards the periphery. The appearance was, Jackson says, "distinct from anything I have ever seen."

There was a "considerable blurring of the optic disks, obviously due to edema," in the patient reported by Russell (Case 99). The right disk showed enlarged and tortuous veins and the arteries were also enlarged. The outer part of the disk showed a remarkable group of small arterioles and enlarged vessels were scattered about the retina. Near the macula was a small patch of pigment, "the result of former chorioiditis." The left disk showed a similar appearance to a lesser degree.

Hemorrhagic glaucoma was reported in one of Geisbock's patients (129).

Double optic neuritis was present in three cases (14, 30, 124).

**Choked Disk.** It will be observed from the foregoing that optic disturbance was present in a number of cases. In only two instances, however—Pfeiffer's case (101) and the author's first case (124)—has choked disk been observed. Behr,<sup>24</sup> in a paper published in 1911, goes very fully into the eye condition in Pfeiffer's patient and says

In the characteristic changes in the fundus we possess a special symptom of marked diagnostic value, and it is to be regretted that only in a very small fraction of the cases reported was the eye examined. All of the cases reported agree that the veins are much dilated and serpentine and dark colored. The arteries are either normal, or in rare cases also dilated and darker than normal. Frequently the retina is livid blue. As a rule the margin of the papilla is distinct, rarely indistinct and never with bulging of the papilla itself. That the blood vessels of the conjunctiva are affected is clear.

Dr. William T. Shoemaker of the Pennsylvania Hospital, Philadelphia, made a very careful examination of the eye grounds in the author's first case (124) and exhibited the patient before the eye section at the College of Physicians. I am indebted to Dr. Shoemaker for permission to quote from his report as follows:

Special interest from an ophthalmic standpoint lies in the violent changes in the optic nerve, retina and blood vessels. These changes are those of typical inflammatory choked disk, identical, it would seem, with those frequently seen with intracranial disturbance.

Carl Behr,<sup>25</sup> in a most important communication on this subject last year, including a case with microscopic examination, says that his case of polycythemia was the first observed with typical choked disk, and while referring to a number of cases of cyanosis in which optic neuritis, blurring of the disk margins, etc., were noted (Hirschberg, Posey, Harms), he is inclined to think that the changes in these cases were not inflammatory but were due to edema, and, in the absence of swelling, represented perhaps the beginning stage of the more pronounced condition.

The retinal changes which Behr demonstrated from his case are enlargement of the veins with no other alteration in the vessel walls than loss of elasticity and thinning. The retinal capillaries showed general distention and irregularity with fusiform dilatations. All of the veins were filled with red cells, but Schlemm's canal, on the other hand, showed no enlargement and contained but a limited number of red cells. There was a general round cell infiltration. The chorioidal vessels were greatly distended and in pronounced cases the sclera may be of a decided bluish color.

Whether or not the case shows simple edema around the nerve head or pronounced choked disk, as in Behr's case (No 101) or in the case which I show (No 124) depends, according to Behr, entirely on the equilibrium maintained in the eyes between the fluid thrown from the blood into the tissues and those carried off through the ordinary lymph channels.

The choked disk in polycythemia, Behr concludes, originates solely from local edema of the papilla and the peripheral end of the optic nerve, and, he states, this choked disk is in no way different ophthalmoscopically and microscopically from that of intracranial origin.

Swan<sup>30</sup> claims that one of the prominent symptoms of polycythemia is exophthalmos. In the cases covered by my summary, however, this symptom was reported in only two instances (Cases 78 and 94).

**Urine** In a majority of the cases the urine showed a small amount of albumin and not infrequently tube casts. In fifty-two cases the urine is not mentioned, in sixteen it was negative or normal, in eighty cases it presented abnormal features as follows

Trace of albumin	Cases 61
Marked albuminuria	8
Tube casts	29
Excess of urobilin	7
Excess of indican	6
Chronic nephritis	4
Sugar	2
Blood	2
Red cells	2
Polyuria	2
Oliguria	1

In addition to the above, urochrome, diacetic acid, acetone, much chromogen, excess of uric acid, leukocytes, diazo reaction (Case 64) eight times the normal amount of iron (Case 113) and a specific gravity of 1,040 were each reported in one case.

**Glandular System** The glandular system appears to have been affected in only six cases. The submaxillary glands were enlarged in one case, the mediastinal glands in one case (124) and the thyroid gland in four cases (25, 31, 63 and 102).

#### BLOOD

**Red Cells** The most important and constant feature of erythremia is the uniform, absolute and persistent increase in the number of erythrocytes in the circulating blood. This increase varies markedly in different patients and in the same patient at different times.

30 Swan Internat Clinics, Philadelphia, 1907, iv, 114

In the vast majority of cases the number of red cells reported ranges between six and eleven million, an average of twenty cases being reported in each increase of a million cells from six to eleven millions. That is, twenty cases reported from six to seven millions, twenty cases from seven to eight millions, etc

The highest recorded counts occurred in Seufert's two cases (63 and 64), which showed 15 000,000 and 15,500,000, respectively. Koester's case (Case 40) showed 13,060,000, and in Gibson and Watson-Wemyss's case (Case 111), 13,250,000 cells were present at one time. Thompson's case (61) exhibited 13,000,000, Myer's case (81) 12,880,000, Englebach and Brown's case (38) 12 584,000. Reckzeh's patient (Case 28) had 12,500,000 red cells, Miller's patient (Case 110) 12,010,000 and four cases (3, 56, 65 and 148) reported counts of 12,000,000, making in all thirteen cases in which counts of twelve million or over occurred.

These higher counts are particularly interesting when one considers Weber's<sup>20</sup> statement that samples of blood showing ten million red cells per cubic centimeter, with coagulation prevented placed in a cylindrical glass, show a corpuscular sediment of over nine-tenths of the whole column, the plasma forming only a thin layer on the surface, whereas normally cells and plasma are about equal.

**Hemoglobin** Notwithstanding the high erythrocyte count, the hemoglobin percentage in most cases was estimated as quite low. It seems probable that the hemoglobin is underestimated in many cases, as in some instances the statement is made by the author that the estimated per cent "is the limit of the scale."

In 111 cases in which the hemoglobin percentage was reported all but four stated the percentage to be 100 or over. These four cases reported 80, 85 and 95 per cent. Sixty-eight cases reported percentages ranging between 100 and 150 and thirty-one cases percentages between 155 and 200. One case reported a percentage of 240 (Case 68).

**Color Index** I have estimated the color index in seventy-nine cases, and, as was to be expected from the comparatively low hemoglobin percentage reported, found it to be between 0.45 and 1.00 in all but ten cases. Of these ten cases six ranged from 1.02 to 1.20 and four from 1.31 to 1.57.

**Microcytes and Macrocytes** Were reported in one case (47).

**Poikilocytes** Present in three cases (28, 33, 47).

**Degenerated Red Cells** Reported in two cases (78 and 79).

**Nucleated Red Cells** Nucleated red cells were present to a very limited extent in twenty cases and to a marked degree in two cases (47, 89), in one of these cases being mostly of the megaloblastic type. A few megaloblasts were also present in three other cases (64, 77 and 79).

**Polychromasia** A tendency of the red cells to stain a lighter or darker blue, known as polychromasia, and said to be found in chronic anemia,<sup>31</sup> was present in three cases (Cases 33, 38 and 47). This condition is regarded by Ehrlich as evidence of degeneration, but, on the other hand, some authorities regard such cells as immature and consequently significant of regeneration.

**Hemolysis** Resistance to hemolysis was reported as slightly increased in one case.

**Color of Blood** Is almost invariably darker than normal.

**Viscosity** The viscosity of the blood is invariably raised whenever the number of red cells per c c is much increased. In one case it was stated as 10.43 (Case 110). Weber<sup>20</sup> found the viscosity of a citrated specimen of the venesection blood in two cases to be more than twice the normal. He says "Supposing the viscosity of normal human blood to be 5.1 to 5.3 (that is to say, 5.1 to 5.3 times that of water), Lommel found the viscosity to be over 11.0 in two cases of polycythemia with splenomegaly, Bence obtained figures varying from 15.9 to 20.9, and Munzer in another case showed figures varying between 12.0 and 23.0 according to the special form of viscosimeter which he employed. In Low and Popper's case the viscosity was 10.4 and in Saundby's case 9.4."

**Coagulation Time** The blood in erythremia undoubtedly coagulates much more quickly than normal blood.<sup>32</sup> In ten cases in which the coagulation time is stated, four (63, 64, 78 and 94) reported coagulation in one minute or less, three (12, 38, 110) a coagulation time of less than four minutes, and three (60, 75, 81) coagulation in from six to ten and a half minutes.

**Oxygen Capacity** The oxygen capacity is stated in but four cases, in one instance (35) being diminished, in another (61) being two and a half times normal, in a third (60) being given as 1,480 c c with a blood volume of 4,765 c c, and in the fourth (110) as 3,375 c c with a blood volume of 10,200 c c.

**Total Volume** According to Weber<sup>33</sup> the normal individual is estimated to possess 4.6 c c of blood per 100 grams of body weight. It is interesting to note that in the eight cases in which the total volume was estimated it very much exceeded the normal.

In Hutchison's two cases (48 and 49) it was greatly increased and in one of his cases reached "the extraordinary figure of 10,750 c c, or more than three times the normal volume for a patient of same weight."

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<sup>31</sup> Butler's *Diagnostics of Internal Medicine*, 1908, p. 617.

<sup>32</sup> Normally coagulation is said to occur in five minutes, although Coplin (*Manual of Pathology*, 1906, p. 404) states that his personal observations indicate that a considerably longer time is usually required.

<sup>33</sup> Weber *Med Chir Tr London*, 1905, lxxviii, 191, and *Tr Med Soc London*, 1907, xxx, 369.



In Miller's case (60) it was 4,765 c c In Thompson's case (61) it was two and a half to three times the normal In Acland's case (50) "the total volume of the blood by the carbon monoxid method was about two and a half times the normal" Weber's case (72) exhibited a total volume of 5,600 to 6,000 c c, while Miller's second case (110) showed a total volume of about 10,200 c c

White, in reporting a case (119), states that the total volume was three times the normal for a man of his weight and calls attention to the fact that "the red cells being double the normal, the patient had six times the normal number of red cells and four times the normal hemoglobin Such blood must have nearly reached a volume which would render circulation very difficult" The specific gravity in this case was given as 1,076

Cryoscopy The cryoscopy finding is given in but two cases, being about normal in one (72) and  $-0.56^{\circ}$  in the other (42)

Glycogen Reaction In one case (73) the glycogen reaction was distinct but not marked

Molecular Concentration Stated in one case (39) as  $-0.56$

Leukocytes Assuming that, as Butler<sup>31</sup> states, the normal variation of leukocytes in health is from five to ten thousand per cubic millimeter it appears that in 27 per cent of the patients there was a moderate leukocytosis (10,000 to 20,000) and in 15 per cent a distinct leukocytosis (over 20,000)

In four cases the white cells are stated as less than 5,000, one case (31) reporting 1,080, which is probably a typographic error

Differential The differential count usually shows some increase in the polynuclear cells, this increase being quite marked in three cases (30, 81, 116) McQuitty's case (102), however, showed a marked decrease in the polynuclear cells and a marked increase in the lymphocytes

The eosinophils were markedly increased in two cases (25, 124), in one of which 20 per cent was reported, and showed some increase in four other cases (18, 20, 41, 74)

Basophils or Mast Cells These cells, which, as Butler<sup>31</sup> states, are found in small numbers in normal blood and more often in leukemia and have as yet no significance, were reported in varying percentages from 0.5 to 4 per cent in thirteen cases

Myelocytes Were present in five cases (76, 77, 79, 90 and 99) in small numbers and in number around 4 per cent in three cases (47, 68 and 144) Blumenthal's case (in doubtful list) showed 36 per cent

#### OUTCOME OF CASES

According to Osler,<sup>23</sup> Vaquez and Quiserne believed that where the polycythemia reached six million it was fatally progressive

In thirty-one of the cases, or 21 per cent, the patient died prior to the date of the report. Three of these patients died as a result of splenectomy (Cases 4, 7 and 93), two from tuberculosis, one as a result of secondary hemorrhage following the removal of a uterine fibroid and two as a result of cerebral hemorrhage.

Four of these patients passed into a comatose condition prior to death, three became paralyzed and others suffered variously prior to death from vomiting, diarrhea, aphasia, blindness, dyspnea, mediastinal pain, jaundice and hemorrhages from the stomach and intestines.

Thirteen cases were reported as showing no marked improvement under treatment, while three patients (Cases 8, 21 and 22) were worse after being under treatment over a period of from three to six years.

Two cases (21 and 80) developed thrombophlebitis and one of these patients also developed a pulmonary infarct.

Some improvement was reported as having occurred in twenty-six cases. In eight of these cases the authors state that the polycythemia increased simultaneously with the general improvement. In only two cases (47 and 94) was marked improvement reported.

#### TREATMENT

With the possible exception of the two cases referred to in the previous paragraph, treatment has been uniformly without permanent benefit.

**Splenectomy** In three cases in which the spleen was removed (4, 7, 93) the patients died in from a few days to six weeks later. In the fourth case (161) the patient died seventeen months later of tuberculosis.

**Venesection** Venesection is reported as having given temporary relief in seven cases. It was performed nine times in two years in Chamber's patient (56) with marked relief on each occasion, but his patient was discharged "in much the same condition as when she entered the hospital."

Venesection was without result in three cases, while in Fuch's patient (27) there was temporary improvement under treatment by venesection and oxygen.

In my experience venesection has been at all times a helpful method of treatment, but unfortunately gave but temporary relief.

**Oxygen** Oxygen was used with some apparent relief in two cases (63 and 64) and was tried without benefit in two cases.

**Arsenic** Tuik (17), Tooth (103) and Miller (110) reported some improvement under arsenic and Levi's patient (98) "left somewhat improved" after treatment by arsenic combined with Roentgen rays. Arsenic, on the other hand, aggravated the symptoms in Watson-Wemyss's case (112) and was without result in six other cases in which it was tried.

**Roentgen Ray** While three cases (33, 47 and 111) showed benefit from the application of the Roentgen rays to the spleen, Case 47 being markedly benefited, this treatment was unsuccessful in six cases

**Faradization** Faradization to the spleen did not materially help Senator's patient (76) and Mackey (Case 42) reports that, while faradization in combination with massage helped the leg weakness, it did not diminish the polycythemia, lessen the cyanosis or prevent gradual enlargement of the liver and spleen

**Diet and Hygiene** In Milchner's patient (113), in whose urine there was eight times the normal amount of iron, a diet containing a minimum of ferruginous material benefited the patient's general condition Senator (76) by dietetic and hygienic treatment apparently benefited his patient at first but later an albumin-poor diet, with other treatment, was without much effect

**Sodium Nitrite** Osler (Case 9), in referring to a patient who had suffered from headache for four years, states that the headaches were cured by the use of sodium nitrite, but that the patient was under observation for only a few months Anders (Case 43), in the case of a female of 25, says that the nitrites gave considerable temporary relief from the beginning

**Sodium Bromid** Was used by Koester (40) for pain in splenic region and headache with some apparent benefit

**General** Nicola reports that under symptomatic treatment, tonics and eliminatives, his patient (Case 77) improved and the cyanosis almost disappeared, but the polycythemia was not affected by the treatment, nor by potassium iodid or x-ray

Carlsbad treatment improved the general condition of Geisbock's patient (Case 31) Inunctions of biniodid of mercury over the spleen, in conjunction with large doses of quinin, resulted in diminution of the size of the spleen and subjective improvement in Begg and Bullmore's case (33), although the polycythemia increased simultaneously with the improvement Biniodid of mercury was reported as being tried without benefit in three other cases

**Treatment Without Success** Various other therapeutic measures, as follows, were tried without especial benefit by different authors

Salicylates, tonics, caffeine, bromids sedatives, nitroglycerin valerianates, hydrastis, iron (two cases), diuretin, quinin (five cases), colonic irrigations (two cases), digitalis, sodium cacodylate, adrenalin chlorid (two cases) thyroid gland, vinegar (two cases), potassium iodid (four cases)

#### AUTOPSIES

Autopsies were reported in twenty-three of the cases

Anemic infarcts were present in the spleen in four cases and yellow nodules in three cases

There was cirrhosis of the liver in two cases

The lungs showed the presence of emphysema in four of the autopsies and contained infarcts in two instances. There was bronchiectasis in one case, hydrothorax in one case; old tuberculosis in one case, and tuberculosis of other viscera in one case

Enlargement of the heart was reported in six autopsies, evidence of old heart disease in two and fibrous myocardium in one

There was evidence of erythropoietic activity of the bone marrow in ten cases, in most instances the bone marrow being described as red and as having lost its fatty tissue. On the other hand, Saundby and Russell (Case 6) stated that the bone marrow in their case appeared normal macroscopically. In one case Rosengart<sup>34</sup> found evidence of leukoblastic and erythroblastic hyperplasia in the liver and spleen

Softening of the brain and cord was reported in four cases.

#### DIAGNOSIS

The presence of polycythemia with cyanosis and enlargement of the spleen, and with symptoms of cerebral congestion, such as vertigo, sense of fulness of the head, etc., is suggestive of erythremia, particularly if the eye-grounds show the marked change so often seen in this condition. The absence of demonstrable splenic enlargement or of cyanosis, or even of both, does not necessarily negative the diagnosis. Broadly speaking, in the light of our present knowledge of the disease, erythremia should be borne in mind in all cases of marked *persistent* and *absolute* polycythemia of *unknown origin*.

It should be remembered that the increase in the red cells must be absolute and persistent and the condition must not be confused with the "relative" increase which is due to decrease in the plasma occurring in those diseases accompanied by a rapid removal of fluid from the tissues, e g, acute diarrhea, dysentery, cholera, etc. Erythremia will be less likely to be confused with relative increase in the red cells if it is borne in mind that in the former condition there is an absence of known cause of diminution in the total volume of the blood. Furthermore, in erythremia the patients are usually more congested in appearance and the increase in the number of red cells is persistent, whereas in relative polycythemia it is temporary. In erythremia the total volume of blood is above the average, in relative polycythemia it is below the average.

It has been claimed that some degree of local relative polycythemia may be induced by obstructing the venous return, the delay allowing a longer time for the blood to leave the vessels, and, according to Weber,<sup>35</sup> impeded circulation may even give rise to general absolute polycythemia

34 Rosengart Mitt u d Grenzgeb d Med u Chir, Jena, 1903, vi, 495

35 Weber Proc Roy Soc Med, London, 1908-9 Clin Sec, p 24

Erythremia must also be differentiated from "erythrocytosis," or *secondary* absolute polycythemia, which condition may be regarded as a compensatory reaction of the organism resulting from some interference with oxygenation

Erythrocytosis is typically seen in congenital heart disease and particularly in congenital pulmonary stenosis, also in chronic diseases of the heart and lungs and in certain individuals residing in high altitudes (Toussy reporting 8,500,000 red cells per cubic millimeter) It has also been reported as a result of chronic acetanilid poisoning (Stengel and White<sup>36</sup>) and in chronic sulphonal poisoning (Fells) (Case 166)

Both erythrocytosis and erythremia appear to be of myelogenous origin, deficiency of oxygenation in the former causing erythroblastic over-activity of the bone marrow, while in erythremia the increase in red cells is apparently the primary condition the stimulating factor being unknown

It is interesting to note that Weil,<sup>37</sup> in 1901, found red bone marrow in two cases of congenital pulmonary stenosis and congenital cyanosis, the normal fatty tissue having almost entirely disappeared, and that Mackey, in 1907, confirmed Weil's findings and pointed out that in a case of chronic cyanosis *without polycythemia* he had found *normal* bone marrow

It has been observed, according to Weber,<sup>38</sup> that there is an increased erythropoietic activity of the bone marrow in animals kept at a high altitude or in an artificially rarefied atmosphere The hemoglobin value as well as the number of red cells is increased and nucleated red cells appear in the circulating blood On the other hand, animals inhaling an excess of oxygen show a decrease in the number of erythrocytes

The same author states that other conditions which may give rise to secondary polycythemia (erythrocytosis), by interfering with proper oxygenation, are (1) experimental stenosis of the superior and inferior vena cava, (2) artificial compression of the thorax, (3) diminution of oxygen and increase of carbonic acid gas in the inspired air, (4) clinical or experimental stenosis of the trachea or larynx, and (5) clinical or experimental pneumothorax According to Weber, Kuhn, by his suction mask (periodical diminution of oxygen pressure in the lungs), was apparently able to produce a decided increase of red cells in some individuals

An increase in red cells is also seen at times in obesity, paralysis of an extremity ether anesthesia and phosphorus poisoning

<sup>36</sup> Stengel and White Univ Penn Med Bull, Phila, 1902 3, 11, 462, Jour Am Med Assn, 1905, 14, 243

<sup>37</sup> Weil Compt rend Soc de biol, June 29, 1901 III, 713

## PROGNOSIS

The disease seems to be progressively but slowly fatal. It has extended in some instances over periods of from ten to fifteen years, but, with the possible exception of two cases (47 and 94), none of the patients so far reported have recovered.

## SUMMARY

In the preparation of the accompanying summary of cases reported in the medical literature, said cases have been tabulated as follows:

Class A—Sixty-nine cases presenting cyanosis and splenomegaly and in which the systolic blood-pressure did not exceed 150.

Class B—Fourteen cases presenting cyanosis and splenomegaly and in which the systolic blood-pressure exceeded 150.

Class C—Forty-two cases with an absence of either cyanosis or splenomegaly and in which the systolic blood-pressure did not exceed 150.

Class D—Twenty-four cases with an absence of either cyanosis or splenomegaly and in which the systolic blood-pressure exceeded 150.

Class E—Thirty cases considered doubtful.

Class F—Ten cases the details of which were received too late for inclusion under proper classification.

Making a total of one hundred and eighty-nine cases.

It is difficult, in the light of our present knowledge of the disease, to establish a hard and fast division between cases of polycythemia, probably secondary in form but of obscure origin, on the one hand, and unquestionable cases of primary polycythemia, or erythremia, on the other. It has, therefore, been the endeavor to include in the summary of cases all of those cases of so-called "polycythemia" in which the etiology of the condition presented a reasonable doubt.

Of the thirty cases included in Class E some appear to be identical with a case reported by some other author and such cases are included in the doubtful list in order to avoid duplicating cases in Classes A to D. Others present certain features of erythremia but sufficient details are not given by the authors to permit of a definite classification. Still others fail to present the essential features of erythremia. It is quite probable that some of the cases included in the doubtful class would prove to be true instances of erythremia had all the facts on which the authors based their diagnoses been set forth in their reports.

For purposes of publication it has been necessary to condense the case reports as much as possible but it has been the aim not to omit any essential features from the condensed report.

In conclusion I wish to express my appreciation of the kindness of Dr. Hobart A. Hare in giving permission to report the two cases described herein, as well as for his suggestions and advice in the preparation of this article. I also wish to thank Dr. E. J. G. Beardsley for his encouragement and assistance in many ways.

320 Hathaway Lane Wynnewood, Pa.

TABLE 1 (CLASS A) —CASES WITH CYANOSIS AND SPLENOMEGALY AND WITH A DISORDER OF THE BLOOD

TABLE I (CLASS 24)		Examination	
Case No. and Author*	History	General cyanosis	Spleen greatly enlarged
1 — Vaquez	Male, aged 40 For ten years dyspepsia, pain in right hypochondrium, cyanosis of the extremities and distention of superficial veins For three years buzzing in ears, with giddiness, lumbar pain and transient hematuria At one time gums swollen and bleeding	Marked cyanosis	Spleen reached to iliac crest
2 — Rendu and Vidal	Male, aged 30 Policeman Illness began with pain in left hypochondrium Two years later large, tender swelling same area Four years later spleen reached to iliac crest Two years later marked cyanosis of face and extremities	Liver somewhat enlarged	Heart normal
3 — Cabot	Female, aged 50, spinster, American, rubber worker Otitis at the age of 18 Several attacks of rheumatism Since menopause at 46, vertigo, palpitation and headache A year ago constipation, possibly due to lead Itching at night Cyanosis of lips for six months	Cyanosis of face and extremities Spleen extended to umbilicus Slight pulmonary systolic murmur Polyuria, trace of albumin, hyaline casts, Conjunctivæ much injected, retinal veins dark and dilated <i>Tâche cérébrale</i> marked	Red cells 12,000,000 Hemoglobin 120 Normoblasts once after venesection Color index 5
4 — Commot	Female, aged 63, single Patient has had increasing pain in splenic region for eight years Attacks of epistaxis since age of 15 Attacks of vertigo and headache for some time	Cyanosis of face Spleen enormous and showed fibrous increase Liver slightly enlarged Heart normal except apical systolic murmur Conjunctivæ dirty Skin pigmented Sub maxillary glands slightly enlarged Urine shows excess of urobilin	Red cells before operation 7,500,000, after operation fell to 5,300,000 Hemoglobin 80 White cells 6,000 No normoblasts

Case No. and Author*	History	General cyanosis	Spleen greatly enlarged	Liver greatly enlarged	Heart normal	Lungs normal	Veins distended	Conjunctivæ injected	Red cells over 8,000,000	Hemoglobin 165	White cells normal	Specific gravity 1.080	Color index 1.03
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4 — Commot	Female, aged 63, single Patient has had increasing pain in splenic region for eight years Attacks of epistaxis since age of 15 Attacks of vertigo and headache for some time	Cyanosis of face	Spleen enormous and showed fibrous increase	Liver slightly enlarged	Heart normal except apical systolic murmur	Conjunctivæ dirty	Skin pigmented	Sub maxillary glands slightly enlarged	Urine shows excess of urobilin				

Case No. and Author*	History	General cyanosis	Spleen greatly enlarged	Liver greatly enlarged	Heart normal	Lungs normal	Veins distended	Conjunctivæ injected	Red cells over 8,000,000	Hemoglobin 165	White cells normal	Specific gravity 1.080	Color index 1.03
1 — Vaquez	Male, aged 40 For ten years dyspepsia, pain in right hypochondrium, cyanosis of the extremities and distention of superficial veins For three years buzzing in ears, with giddiness, lumbar pain and transient hematuria At one time gums swollen and bleeding	Marked cyanosis	Spleen reached to iliac crest	Liver somewhat enlarged	Heart normal				Red cells 6,200,000, later 5,250,000	White cells 4,500	No nucleated red cells		
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Case No. and Author*	History	General
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Spleen removed and patient died of sepsis six weeks later Note that even with the high blood count before operation the hemoglobin estimated at only 80 Autopsy In addition to septic changes in the abdomen, carries of spinal column were discovered

Four years later skin bronzed and gums spongy and bleeding

Patient died following year of acute tuberculosis Vaquez regarded case as congenital heart disease until autopsy revealed absence of organic heart involvement Autopsy Enlarged spleen and liver Absence of cardiac disease Spleen weighed 1,800 gm and liver 2,800 gm Died with increase of dyspnea Autopsy Spleen hard, fibrous and firmly attached by old adhesions to surrounding structures It contained large caseous areas and weighed 4,000 gm Tuberculosis present in other viscera Heart normal Bone marrow thought to show evidence of over activity

No treatment or outcome mentioned

5.—Mc  
Keen

Male, aged 53, German, packer in iron foundry. For twenty years attacks of dyspnea at intervals. Cyanosis for eighteen months, dating from dyspneic attack. Attacks of vertigo and blurring of vision and sweating every two or three days

Extreme cyanosis of face, extremities and tongue, and especially lips, tip of nose, ears, hands and feet. Spleen 2 inches below costal margin. Liver 2 inches below ribs. Lungs dullness 2 inches below ribs. Lungs emphysematous. Heart sounds clear, pulse tension not high. Gums swollen and bleeding. Eyes congested, retinal veins engorged with dark blood. Fingers slightly clubbed. Urine trace albumin, blood and granular casts.

Intense cyanosis face and extremities. Spleen reached to below umbilicus. Liver much below ribs. Lungs showed impaired resonance and impaired breath sounds at bases. Accentuated pulmonary second sound, pulse regular, full and high tension. Injected conjunctivæ. Clubbed fingers. Mentalitv poor. Knee-jerks absent. Urine showed cloud of albumin, a few hyaline casts and an excess of indican

Male, aged 54, electroplater. Mother died from phthisis. Patient had gastric fever and lues as a young man. At 46 had influenza and spleen reached to umbilicus. Was then well for six years when began have abdominal pain, headache and great muscular weakness with loss of flesh

6.—Saundby  
and  
Russell

Female, aged 44

7.—Van  
der  
Weyde  
and Van  
Ijveren

Male, aged 35, Hebrew, tailor. No previous illness. Cyanosed for years. Constipation and vomiting for two years. Later hæmorrhage and pain in left side

Cyanosis very marked. Spleen not palpable but gave four inches of vertical dulness. Blood pressure 125. Urine showed trace of albumin and a few granular casts.

Red cells 9,380,000 to 9,840,000. Hemoglobin 120 plus. White cells 9,600. Polynuclears 74 per cent, small lymphocytes 18 per cent, large lymphocytes 6 per cent, eosinophils 2 per cent. Color index 0.6

Patient died soon after, comatose, jaundiced and more cyanosed. Russell saw this patient with enlarged spleen several years before any cyanosis was observed. Autopsy. Spleen 1,361 gm., appeared normal on section. Considerable mucopurulent secretion in bronchial tubes. Heart somewhat enlarged, left ventricle thickened, evidence of some old mitral disease. Viscera congested. Marrow of femur appeared normal macroscopically.

Splenectomy performed and patient died twenty-five days later. Note low hemoglobin estimation. Autopsy. Veins of spleen undergoing fibrosis. Dilated portal circulation greatly dilated. Portal vein thrombosed. Hepaticoduodenal ligament thickened from old inflammation. Kidneys normal. After being under observation and treatment for three years seemed rather worse.

Red cells 7,000,000 to 9,000,000. Hemoglobin 140. White cells normal. Color index 0.87

Red cells 7,600,000. Hemoglobin 90-95. White cells 12,800. Polynuclear neutrophils 84.7 per cent. No methemoglobin. Color index 0.6

Red cells 6,500,000 to 10,000,000. Hemoglobin 125. White cells 8,000 to 30,000. Differential normal. Specific gravity 1.068 to 1.080. Coagulation time 1½ minutes. Color index 63 to 96



TABLE 1 — (Continued)

Case No and Author*	History	Examination	Blood Examination		Outcome, Treatment, Autopsy and Remarks
			Red cells	Hemo- globin	
9 — Osler	Female, aged 44 Previously healthy Has two healthy children Cyanosis for many years Headache and fail- ing vision for past four years	Marked general cyanosis Spleen 3 inches below costal margin Liver, lungs and heart normal Pulse high tension Urine showed trace of albu- min and a few hyaline and granular casts	11,616,000 120 White cells 5,000 Specific gravity 1.067 Color index 0.5		Patient under observation for only a few months Headaches cured by sodium nitrate
10 — Osler	Male, aged 46, Hebrew, shoemaker For 20 years slight cough and pains in chest For six years failing strength Cyanosis for four years Pains in abdomen and legs and occasional attacks of dyspnea for three years	Very marked cyanosis Spleen not felt but moderately enlarged at autopsy Liver 2 inches below costal margin Lungs emphysematous Heart en- larged Veins full Vessels of fundus oculi congested and tortuous Skin pigmented Urine shows trace of albumin	Red cells 8,250,000 White cells 8,300 Differential nor- mal		The cyanosis rivalled that of congen- ital heart disease, the patient being known as "the blue baby" Patient died with drowsiness and collapse Autopsy Spleen moderately en- larged Lungs somewhat emphyse- matous Heart about normal Full notes not available
11 — Rosen- gart	Male, aged 41 Pain in stomach, vom- iting, giddiness, weakness, wasting and dyspnea on exertion Enlarge- ment of spleen noted four years ago after an attack of measles	Well marked cyanosis Greatly en- larged spleen Liver moderately enlarged Lungs normal Heart en- larged and shows systolic murmur Blood pressure increased	Red cells 10,000,000 Hemo- globin 190 White cells 12,- 000 Specific gravity 1.072 Blood dark and viscid Color index 0.95		
12 — Col- lins	Female, aged 24, Irish, servant Three years ago began to have pain in the left side, cyanosis, giddiness, con- stipation and occasional headache, vomiting and epistaxis Six months ago left foot blue and swollen for a fortnight Symptoms subsided some- what in summer Menses normal	Startling cyanosis of face and extremi- ties Spleen extends from 2 inches below axilla to within 3 inches of iliac crest Liver not enlarged Lungs normal, but dyspnea on exer- tion Heart normal Pulse high ten- sion Conjunctivæ injected Some pigmentation of skin Urine normal	Red cells about 10,000,000 Hemoglobin 110 White cells 17,800 Differential normal Blood dark and flows slowly, coagulating in less than four minutes Color index 0.55		Hall's case (number 163) is possibly a duplication of this case
13 — Turk	Female, aged 45, Polish Jewess Pa- tient at age of climacteric	Extraordinary cyanosis Spleen con- siderably enlarged Lungs normal Heart normal except accentuated aortic second sound Veins promi- nent and arteriæ thickened Con- junctivæ injected	Red cells 9,985,000 Hemo- globin 140 White cells 33,- 800 Blood very dark and viscid Color index 0.7		
14 — Turk	Female, aged 43, laundress No hered- itary taint, Five children Erysipe- las three years ago Phlebitis of left leg five months ago Attack of head- ache and giddiness with right facial paralysis a month ago	Extraordinary cyanosis Spleen en- larged Heart hypertrophied Veins distended Double neuro retinitis Urine shows cloud of albumin and epithelial and other casts	Red cells 7,500,000 Hemo- globin 112 Color index 0.75		Patient died a few weeks later, coma- tose, with failing heart and edema of the lungs Autopsy Spleen en- larged and showed multiple anemic infarcts All viscera engorged with dark blood Marked parenchyma- tous nephritis and hypertrophy of left ventricle

15—Turk

Female, aged 60 Two years ago had up for five months with pain, swelling and blueness of right foot Since then has had a similar condition of left foot and right hand

General cyanosis Spleen reaches inch below umbilicus Liver slightly enlarged Slight bronchitis and emphysema Heart slightly enlarged Distended capillaries, vessels thickened Conjunctivæ injected Urine shows cloud of albumin and a few hyaline casts

Red cells 8,220,000 to 10,630,000 Hemoglobin 180 White cells 12,000 to 19,000 Some excess of polynucleus and a very few nucleated cells Color index 0.9

16—Turk

Male, aged 44, weaver Ten years ago pain in left hypochondrium, fever, wasting and enlarged spleen Four years ago similar illness Recovered both times after taking quinin but for some months past complained of pain in left hypochondrium and general weakness

Cyanosis of face Spleen reaches 2 inches below umbilicus Liver reaches to umbilicus Lungs normal Heart normal Distended veins Blood-pressure 115 Conjunctivæ injected Urine shows albumin but no casts

Red cells 8,430,000 to 9,670,000 White cells 26,700 Polynucleus somewhat increased A very few nucleated red cells Mast cells somewhat increased Sp gr 1.070

17—Turk

Female, aged 33 Three years ago began to have pain in left hypochondrium and soon afterwards spleen found to be enlarged

Patient improved somewhat on arsenic, spleen becoming a little smaller and the red cells dropping to about 7,000,000

18—  
Preiss

Male, aged 49 Painless enlargement of spleen for seven years Erysipelas right arm three and a half years ago, followed by thrombosis left iliac vein Palpitation and dyspnea for past year

Red cells about 7,000,000 Hemoglobin 120 to 150 White cells 16,000 to 26,000 Relative increase polyeosin and mast cells A few nucleated reds Sp gr 1.068

Large uterine fibroid removed and patient died of secondary hemorrhage following operation Autopsy Spleen showed marked excess eosinophilous cells but no erythroblasts Bone marrow in state hemopoietic over activity All viscera engorged Peritoneal cavity contained large quantity of blood

19—  
Bauer

Female, aged 50 For some years attacks of indigestion and faintness with marked cyanosis of skin and mucous membranes

\*For references see text

TABLE 1 — (Continued)

Case No and Author*	History	Examination	Outcome, Treatment, Autopsy and Remarks	
			Blood Examination	
20 — Vaquez and Laubrey	Male, aged 60 Obitus at 21 Malaria at chest above nipple level Spleen extends below umbilicus Liver normal Heart normal Some edema of left chest wall Conjunctivæ injected Mentality slow Urine shows trace of albumin	Marked cyanosis of face, hands and chest above nipple level Spleen extends below umbilicus Liver normal Heart normal Some edema of left chest wall Conjunctivæ injected Mentality slow Urine shows trace of albumin	Reds about 8,000,000 Hemoglobin 160 180 White cells 14,000 Relative increase of polys and eosinoph A few nucleated reds Resistance hemolysis slightly diminished Color index 1 00 to 1 12	Two years later thrombo phlebitis left leg and signs infarct in lung Six years after first examination edema with distention veins both legs, arteries rigid, conjunctivæ injected, cloud albumin in urine, also red cells and casts Recently patient tapped three times for ascites
21 — Weintraud	Male, aged 31 Measles and typhoid in childhood From 18 to 20 paroxysmal pain in abdomen and chest, urine being dark brownish red after each paroxysm For 17 years liable to frequent migraine like attacks, recently more severe and associated with paraphasia and enlargement of spleen At 29 more abdominal pain, spleen larger and albumin in urine At 31 examined account of swelling of feet	Cyanosis of face Spleen reaches to within 2 inches of iliac crest Liver 2 inches below costal margin Lungs normal Heart normal Urine shows cloud of albumin but no casts	Red cells over 8,000,000 Hemoglobin 110 Six years later red cells 7,880,000 Hemoglobin 130 White cells 13,000 Relative increase of polys, nucleated reds rare Sp gr 1,057 Color index 0 69 to 0 81	Present condition (four years later) the same except that spleen is larger
22 — Weintraud	Male, aged 46 Syphilis at 19 Diphtheria at 29 Remained well until four years ago when he began to have daily attacks of headache with giddiness, vomiting and disturbance of vision and right hand became congested and swollen	Marked cyanosis of face Spleen reached below umbilicus Right lungs and heart normal Left but pulse much smaller than left but nothing in chest to account for difference Urine shows albumin but no casts	Red cells nearly 10,000,000 White cells 30,000 Polys relatively increased A very few nucleated reds	
23 — Jamieson	Female, aged 26 Complained of cough, dyspnea, palpitation and pain in hypochondrium	Cyanosis of face and extremities Spleen enlarged Subcrepitant râles at base of lungs, prolonged expiration, sibilant râles over rest of lungs Heart rapid Urine decreased in quantity two gm albumin to the liter	Red cells 7,200,000 Hemoglobin 105 White cells 10,100 No nucleated red cells Differential normal Color index 0 73	
24 — Hitchcock	Female, aged 43 Severe pain in left hypochondrium five years ago and again 18 months ago, when noticed large swelling in left hypochondrium	Marked cyanosis face and extremities Spleen enlarged and hard Liver enlarged and hard Lungs and heart normal Pulse full and strong Urine shows albumin but no casts	Red cells greatly increased Hemoglobin 170 White cells normal	

25 — Ascoli	Male, aged 20, carpenter Malaria at age of 8 At age of 15 epigastric and precordial pain and dyspnea At 18 severe and prolonged febrile attack with violent delirium, excessive sweating, thirst and intense redness of face and neck Attack left him very weak and subject to severe pain in the epigastrium	Face brown and cyanosed Spleen palpable Lungs and heart normal Irregular pigmentation of abdomen Enlargement of thyroid Urine shows trace of albumin, urobilin and some casts	Red cells 7,200,000 Hemoglobin 95 White cells 15,000 No nucleated reds Eosinophils 20 per cent Color index 0.66	Patient improved while in hospital On one occasion radial blood showed 6,100,000 red cells while capillary blood from ear showed 6,000,000 Comparison with other cases suggested to Weber a toxemic factor in this case
26 — Kraus	Male, aged 59, porter For four years headache, disturbed sleep, palpitation and dyspnea A few weeks ago had diarrhea	General cyanosis, most marked in face and extremities Spleen considerably enlarged Liver slightly enlarged Heart enlarged Blood-pressure normal Urine shows albumin and a few hyaline and granular casts	Red cells 10,800,000 Hemoglobin 120 White cells 10,200 Blood almost black Sp gr 1.071 Viscosity increased No nucleated reds Differential about normal Color index 0.55	This is apparently the same case which was reported by Reckzeh (see Case 154)
27 — Fuchs	Male, aged 42 Only a short society report, no history Marked symptoms are cyanosis, headache, vertigo and bloody stools	Cyanosis of face, extremities, tongue and mucous membrane of mouth Spleen and liver enlarged Urine shows albumin	Red cells increased but number not stated	Venesection and inhalations of oxygen gave temporary improvement
28 — Reckzeh	Male, aged 34 Mother died of tuberculous Prior to 1894 patient had measles, scarlet fever, otitis media, meningitis, pneumonia (twice), sciatica, inflammation of left shoulder, catarrh of lungs, gonorrhea and syphilis In 1896 hematemesis, and soon afterward began to suffer from headache, giddiness, lassitude, and pain under left costal arch	In 1899 Face cyanosed Spleen to iliac crest Lungs and heart normal Urine showed trace of albumin but no casts In 1902 Still very cyanosed Spleen to within 1½ inches of pubis Urine 700 to 3,000 c c daily, Sp Gt 1.010-1.018	Red cells varied from 8,300,000 in March, 1899, to 12,500,000 four weeks later, dropping to 6,500,000 three years later Hemoglobin 150, three years later 125 White cells averaged 24,000 Sp gr 1.080 Blood from ear almost black A few poikilocytes	Treatment by punctions
29 — Zimblek	Male, aged 32 For years liable to headache, colds in head, sore eyes, rheumatic pains and bleeding from nose and gums on slightest provocation When first seen complained of intense pain in left hypochondrium due to enlarged and tender spleen	When first seen Moderate cyanosis of face and hands Spleen large and tender Lungs and heart normal Urine showed albumin but no casts A few weeks later Patient became depressed Cyanosis increased Transient edema right arm and hand Liver moderately enlarged, heart somewhat dilated Albumin and hyaline casts	Red cells about 9,000,000 Hemoglobin 120 White cells 13,000 to 20,000 Relative increase of polys Color index 0.66	Soon after last examination patient fell to the floor unconscious, left side being paralyzed and died the following day No autopsy

\*For references see text

TABLE 1 — (Continued)

Case No and Author*	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
30 — Pruves Stewart	Female, aged 53 Five years ago headache, vomiting and giddiness with marked weakness of extremities, attack lasting a week Three years ago similar attack, lasting six months and leaving her permanently weak and unable to work A year ago pain, redness and swelling left side of abdomen Pain passed off and did not return Five weeks ago intense headache, dimness of vision (more marked in right eye) and vomiting without reference to food Occasional blood in vomitus Considerable loss of weight during five years	Lips cyanosed, face flushed, with dilated venules, tongue and buccal mucosa bright red, hands and feet always warm and persistently flushed, numerous bright red nevroid elevations over trunk Spleen two inches below umbilicus Liver enlarged Accentuated aortic second sound, pulse high tension, arteries thickened, veins of abdomen markedly dilated and tortuous Skin dry Double optic neuritis with retinal hemorrhages Urine, Sp Gr 1.024, laden with albumin and showing granular, hyaline and cell casts	Red cells 8,750,000 to 10,000,000 Hemoglobin 130 White cells 24,000 Polys 94 per cent Monomorphs 6 per cent Blood very dark and viscid Color index 0.65 to 0.74	Patient after leaving hospital had an attack of right hemiplegia with aphasia, apparently having a cerebral hemorrhage Gradually became totally blind in both eyes Aphasia passed off but hemiplegia persisted Died soon after (about five months after first seen by Stewart) No autopsy could be obtained
31 — Geisbock	Male, aged 51 Apparent recovery from severe jaundice, then headache, giddiness and loss of appetite and weight	Face somewhat cyanosed Spleen enlarged Liver enlarged Lungs and heart normal Blood pressure 100 to 110 Slight goiter Urine showed occasional traces of albumin and a few tube casts	Red cells 9,000,000 Hemoglobin 200 White cells only 1,080 (possibly a typographic error) Color index 1.11	Venesection of 200 cc scarcely relieved headache, nor did application Roentgen rays to spleen improve general condition Carlsbad treatment had a better effect Geisbock thought this case resembled some of those described by Turk
32 — Mun Koski	Male, aged 22 Remarkably cyanotic from early childhood Came under observation for cyst in capsule of right kidney which was operated on successfully	Remarkably cyanotic Spleen enlarged No heart disease	Polycythemia present	
33 —Begg, Bulmore and Horder	Female, aged 47 Phthisical family history Always suffered from constipation and migraine like attacks Liable to epistaxis Complaints of swelling in left abdomen, lingual and loss of weight	Marked cyanosis of face and hands Spleen extends 2 inches below umbilicus Liver not enlarged Lungs and heart normal Varicose veins of legs Urine normal	Red cells 6,850,000 Hemoglobin 100 White cells 11,300 Polys 77.3 per cent A few nucleated reds No myeloblasts About four normoblasts to the thousand white cells Sp gr 1.054 Well marked poikilocytosis and polychromatophilia Color index 0.73	Inunctions binoid mercury over spleen (part being exposed to anti-facial heat) and large doses quinin resulted in diminished size spleen and subjective improvement Later good results from Roentgen rays to spleen Polycythemia, however, increased simultaneously with general improvement (compare with Hann's case—Case 108)

Inch-  
son  
and  
Miller

Male, aged 45, farm laborer Seven years ago fit with unconsciousness, 3½ years ago carbuncle Six months ago stomatitis, dyspepsia and constipation followed by vomiting, giddiness and loss of weight A few weeks later spleen enlarged Late hematemesis, increased giddiness and twitching of face Patient finally became quite blind but nothing found in optic disks beyond slight hyperemia and engorgement

Cyanosis of face, lips and nose deep purple Spleen reached to umbilicus Liver not enlarged Lungs normal Heart displaced upwards but sounds clear Vessels thickened Blood-pressure 145 Gums swollen and bleeding Optic disks show slight hyperemia and engorgement Urine shows trace of albumin

Red cells 8,000,000 to 11,000,000 Hemoglobin 120 White cells 17,000 to 22,000 Relative excess of polys No nucleated reds Viscosity increased Color index 0.54 to 0.75

Seven years and two months after first attack patient died in coma with hyperpyrexia Autopsy Spleen 38 ounces, hard and irregular, many yellow areas and irregular infarcts but no tubercles Dense adhesions between liver, spleen and diaphragm Heart 12½ ounces, valves normal, myocardium fibrous Intense congestion everywhere Left lenticular nucleus and right optic thalamus red and disintegrated Bone marrow red and disintegrated ally showed changes and microscopic-erythroblastic activity

35 —  
Lom-  
mel

Male, aged 42, bricklayer Three years ago began suddenly to have pain in abdomen, headache and giddiness A month later face became very red and has remained so Abdominal pain has grown steadily worse

General cyanosis, most marked in the face and hands Spleen 3 inches below costal margin Liver moderately enlarged Lungs and heart normal Veins distended Blood pressure 125 Conjunctivae injected Urine shows trace of albumin

Red cells 8,300,000 to 8,600,000 Hemoglobin 140 White cells 11,000 Differential normal Nucleated red cells very rare Blood very dark and viscosity increased Oxygen capacity diminished Specific gravity 1.068 Color index 0.83

Patient died six months later after developing severe abdominal pain, rapid loss of weight, jaundice and, finally, profuse hemorrhage of stomach and intestines Venesection had been repeatedly performed (150 to 200 cc) with temporary subjective relief Autopsy Spleen adherent and contained scattered yellow nodules Liver smooth, ante-mortem thrombi in portal system, hepaticoduodenal ligament congested, hepaticovenous angiomata Lungs congested Heart slightly enlarged Stomach and intestines contained dark fluid blood, mucosa blue and swollen Bone marrow had lost fat cells Patient died shortly after examination with paralysis of right side and great dyspnea Autopsy Spleen showed scattered yellow patches of ischemia Lungs congested, showing several infarcts Heart dilated and hypertrophied Bone marrow showed dark bluish red areas of erythroblastic tissue replacing fat cells Brain congested and edematous, cord degenerated

Red cells 10,000,000 to 11,500,000 Hemoglobin 90 White cells 7,000 Differential normal No nucleated reds Viscosity much increased Color index 0.39 to 0.45

General cyanosis, most marked in face Spleen 3 inches below costal margin Liver 3 inches below costal margin Slight bronchitis Heart sounds weak Veins distended Blood pressure 110 Marked edema of legs and feet Symptoms of tubes dorsalis Urine shows albumin and some hyaline casts

36 —  
Glues-  
ner

Male, aged 41, shoemaker Syphilis at 24 Pain in left abdomen for fourteen years Headache for seven years Redness of face two years Pain and swelling in legs for four months Late anorexia and constipation

\*For references see text

TABLE 1 — (Continued)

Case No and Author*	History	Examination		Blood Examination	Outcome, Treatment, Autopsy and Remarks
		Cyanosis of face	Spleen enlarged	Red cells 10,800,000	
37 — Schminsky	Male, aged 42 Has had pneumonia Two years ago pyelitis Since then face has become dark red Complains of dyspepsia, constipation, erythroid melalgic symptoms, loss of flesh, general weakness and vertigo	Liver much enlarged	Cutaneous veins dilated	White cells 12,800 Polys 81.7 per cent, large mono 4.2 per cent, small mono 3.8 per cent, eosino 3.6 per cent, No nucleated reds, no polkilocytes Color index 0.74	Duration eleven years Treatment entirely without success Quinin increased vertigo and headache Salicylates iron and tonics, caffeine, bromids, sedatives, nitroglycerin, valerianates, hydrastis, Fowler's solution, etc, all tried without any special improvement Three or four exposures over spleen, of five minutes duration, produced no change in either symptoms or blood findings Myer (Bull St Louis Med Soc, Dec 15, 1910, iv, p 451), speaking of this case, states that two months prior to patient's death she suffered the most intense pain in the mediastinal region from the cardiac to the pharynx, also in extremities A month prior to her death she was greatly emaciated and unable to take food Her face was markedly cyanotic up to the last Senator in his article goes very fully into the findings of a number of blood examinations, including re fraction value of serum, amount dry residue, etc
	Female, aged 40, Russian Jewess, housewife For ten years chronic headache, vertigo and diffuse redness of skin Five years ago "sudden rush of blood to head," extreme vertigo and excruciating headache, the attack lasting one minute and succeeded by syncopeal sensation without unconsciousness and followed by general weakness At about this time lump appeared in side Three years ago, following extraction of teeth, had prolonged hemorrhage and severe clamps in legs Two years ago abdominal pain, headache, anorexia and menstrual disturbances	Mild diffuse cyanosis, lips purplish, tongue red and gums and mucosæ dusky red, toes slightly cyanosed and cold Spleen tender on pressure and reaches mid line and to level of umbilicus Liver finger breadth below costal margin Lungs normal Heart somewhat enlarged Venules dilated Blood pressure 135 to 140 Conjunctivæ injected Fundus oculi dark red and veins large and dark blue Tenderness over sternum and superficial bones and scalp Hemorrhoids present Urine shows trace of albumin	Face and mucous membranes dark red Spleen much enlarged No fever Glands not enlarged Blood pressure 145 Urine shows a trace of albumin	Red cells 7,316,000 to 10,200,000 Hemoglobin 122 to 185 White cells 5,600 to 20,500 Polys 73.8 per cent, Mononuc 3.5 per cent, Lymphocytes 18.8 per cent, Eosino 3.5 per cent, Mast cells 0.5 per cent A few normoblasts Viscosity much increased Molecular concentration 0.56	
38 — Englebach and Brown	Male, aged 40, workman Father died of tuberculosis, mother of dropsy Diphtheria in childhood Six years ago took cold and had fever, cough, expectoration, with some blood (never large hemorrhage), stinging pain in chest and night sweats Also pain in left abdomen which still persists Denies venereal infection Formerly drank much whiskey but not much beer				

Male, aged 44 In 1904 first noticed that gums bled on slight provocation Complained of headache, vertigo, constipation, pain in abdomen and darkening of vision (coming on suddenly)

Cyanosis appeared while under observation Spleen moderately enlarged Arteries sclerotic Urine shows some albumin Eyes see "Remarks"

Red cells 13,060,000 White cells 9,800 No abnormal cells in stained preparation

Treatment normal salt solution and sugar per rectum and sodium bromid for pain in splenic region, headache decreased Inhalations oxygen given but cyanosis soon developed with headache, vomiting, etc Treatment continued, however, and patient improved and is again able to work Jackson (Ophthalmology, Milwaukee, 1907, iv, No 1) says this case showed some disturbing attacks in retinal circulation causing attacks monocular blurring of vision

Female, aged 45, washerwoman For two years cyanosis of face and hands For one year abdominal pain and anorexia For past two months attacks of giddiness, vomiting and heaviness of feet

Male, aged 51, English, laborer in iron foundry Father died of "stroke," mother of dropsy Patient drinks beer freely Three years ago influenza, followed by legs becoming blue, swollen and painful For two years cyanosis, distended veins, pain and weakness in legs and inability to work For one year enlarged spleen and liver, edema of legs, abdomen and thoracic wall, and albumin, indican and urobilin in urine Constipation present

Well marked cyanosis of face and hands Spleen 3 inches below costal margin Liver 3 inches below costal margin Lungs and heart normal Pulse high tension Conjunctivæ injected Urine normal

Face, ears, nose, mouth and pharynx dark red, rest of body bluish red, feet and legs almost purple, hands only slightly tinted Spleen extends to umbilicus in mid line and to seventh rib in mid axillary line Liver smooth, firm and not tender, reaches to umbilicus Shortness of breath on exertion but no giddiness Heart enlarged Blood-pressure 140 Conjunctivæ injected, ophthalmoscope shows fulness and broadening of the veins of the fundus oculi No edema, nor soreness or bleeding of gums

Red cells 7,300,000 Hemoglobin greatly increased White cells 6,400 Moderate relative increases of eosinophiles A few nucleated reds Viscosity greatly increased

Two years ago hemoglobin 170, white cells 4,200 to 13,000 One year ago red cells over 8,000,000 At present red cells from 6,500,000 to 9,600,000 Polys 81 per cent, lymphoc 15.4 per cent, hyaline 2.6 per cent, eosin 1.0 per cent Velocity normal Viscosity increased (visc 9.4) Blood very dark Sp gr 1.067 to 1.080 Cytoscopy —0.56 deg C No nucleated reds No microcytes or poikilocytes

Digitalis and squill removed edema Liquor arsenicalis, quinin sulphate, irrigations of colon with alpha naphthol solution, adrenalin chlorid, thyroid gland, vinegar, K I, and bimodid of mercury all tried without benefit Erythrol tetranitrate benefited him but had to be discontinued account giddiness Massage and faradism helped leg weakness as did also elastic bandage Treatment has not diminished polycythemia, lessened cyanosis nor prevented gradual enlargement of spleen and liver



TABLE 1 — (Continued)

Case No and Author *	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
43 — Anders	Female, aged 25, single Family history of Bright's disease, eczema, rheumatism, moderate obesity, organic heart disease and hemophilia Personal history of measles and colds Eyes bad since age of 10 Epistaxis 11 to 23 Cyanosis, slowly increasing, first noted at 15 Congestion of lungs at 17 Rheumatism and severe headaches since 17 For several years timid, mentally distressed and apprehensive For past year headaches better, cyanosis worse, and violent cramps in legs and feet and slight vertigo at intervals Menstruation, formerly painful, is now irregular	Face markedly cyanotic except around mouth, chin, base of ears and a narrow border around both eyes, mucous membranes somewhat less livid Spleen slightly enlarged Liver not enlarged Heart rapid (110 to 120), slight enlargement of left ventricle, second aortic sound slightly accentuated Superficial veins lack tone Blood pressure 145 Thyroid normal Urine usually negative but showed sugar (less than 1 per cent) on one occasion Height 5 feet 6 inches Weight 198½ pounds	Red cells 5,300,000 to 6,960,000 Hemoglobin 110 White cells 13,600 to 20,000 Mostly polys Red cells stain normally and are of normal size and form	Treatment directed toward reestablishment menstrual function For past two and a half years there have been recurring exacerbations and remissions Headaches practically absent for over a year, or since menses more nearly normal Apprehension and cyanosis noticeably improved during last six months and now (Jan, 1907) nervous tremor, apprehension and endurance markedly improved Nitrites gave considerable temporary relief from headaches from beginning, showing cause of headaches to be, in part, at least, heightened tension in cerebral vessels
44 — Anders	Male, aged 31, clerk Indigestion for 15 years Vision blurred at times Headaches, mental apprehension and slight dizziness have been chief nervous phenomena Cyanosis for five years Easily tired for several years	Cyanosis of the lips, conjunctivæ, ears and face and especially the nose, hands and feet also quite dusky Spleen slightly enlarged Left ventricle somewhat hypertrophied, faint systolic murmur at apex, second pulmonary sound moderately accentuated Pulse accelerated, tension not high Urine negative Height 5 feet 9 inches Weight 125 pounds	Red cells 7,400,000 Hemoglobin 130 White cells 12,600 Polys 69 per cent, small lymph 24 per cent, large lymph 6½ per cent, eosin 0.5 per cent No polkilocytes, macrocytes, microcytes or nucleated reds Red cells uniform diameter, perfect contour and stain well Color index 0.88	Digestion improved under treatment, but cyanosis and nervous phenomena not relieved Digitalis, strychnin and nitrites afforded only temporary relief
45 — Wes tenooffer and Linsch- feld	Male, aged 28 Supposed to be suffering from meningitis No blood count made during life but autopsy suggests strongly the existence of polycythemia	Cyanosis present Spleen enlarged	Autopsy Spleen large, due chiefly to engorgement Malpighian corpuscles smaller than average, the slight myeloid transformation was leukoblastic, erythroblasts being present only in very small numbers, very few cells containing phagocytes seen Cerebral hemorrhage but no meningitis, viscera and bone marrow extremely engorged, all cellular elements of marrow increased, white cells more than erythroblasts Normal fat entirely disappeared While nucleated reds not relatively in excess, the total number in bone marrow must have been enormously increased	

16 —

Stu-  
berg

Male, aged 18, workman In 1904 re-  
ceived a blow on the head but no  
unconsciousness or vomiting Since  
then headache and later vertigo

17 —

Aldrich  
and  
Crum-  
mer

Female, aged 53 Mother died of tuber-  
culosis For eight years patient has  
had striking redness of face (was  
called "the red Indian woman"),  
fullness of head and occasional ver-  
tigo Three years ago noted tumor  
in abdomen A year ago complained  
of dizziness, extreme fatigue, feel-  
ing of weight in abdomen and pres-  
sure over bladder, slight nausea and  
occasional diarrhea No fever or  
loss of weight

Cyanosis of face Spleen enlarged and  
vein firm Conjunctivæ injected  
Blood-pressure 140 to 145 Mod-  
erate albuminuria

Exposed skin dusky red with enlarged  
veins Spleen extends 1 inch to right  
of umbilicus and down beyond crest  
of ilium Liver not enlarged Lungs  
slightly emphysematous Heart nor-  
mal Conjunctivæ injected Urine  
negative

Red cells 6,272,000 to 7,264,-  
000 Hemoglobin 120 White  
cells 4,860 to 7,300 Neutro-  
phils 73 per cent, lympho-  
cytes 16 per cent,

Red cells 7,700,000 Hemo-  
globin 120 White cells 4,-  
700 Polys 72.5 per cent, S

Lymph 8.0 per cent, S  
lymph 11.0 per cent, S  
4.0 per cent, myelocyt 4.5  
per cent Many microcytes  
and a few macrocytes, some  
poikilocytosis and poly-  
chromatosis Considerable  
number of nucleated reds  
(24 in a count of 200 white  
cells), mostly all of megal-  
oblastic type Color index  
0.78

Total volume of the blood was  
greatly increased and in one  
of these cases it reached  
"the extraordinary figure of  
10,750 c c, or more than  
three times the normal  
amount for a patient of  
same weight"  
See "History"

No treatment mentioned but author  
thinks that condition was not due  
to trauma

Aisense tried but had to be discon-  
tinued Tumor was regularly given  
fifteen minutes exposure to Roent-  
gen ray, after eleventh exposure  
symptoms practically disappeared,  
tumor being smaller and red cells  
fell to 6,048,000, hemoglobin to 90,  
microscopic findings about as before  
At present, a year later, no further  
blood-examinations have been made  
but report from patient indicates  
continuing improvement Aldrich  
and Crummer call attention to this  
being one of the few cases showing  
definite improvement  
Apparently no detailed report has been  
made of these cases

Apparently no detailed report has  
been made of this case

18 and 19

Hutchi-  
son

Two cases referred to by Weber as  
having come under the observation  
of Dr R Hutchison at the London  
Hospital Weber says they were  
typical cases of "splenomegalic poly-  
cythemia" but gives no details other  
than as stated under "Blood Exami-  
nation"

50 —

Acland

Weber says "I have Dr Acland's per-  
mission to state that in an as yet  
unpublished case of splenomegalic  
polycythemia under his care at the  
St Thomas Hospital a clinical esti-  
mation of the total volume of the  
blood by the carbon monoxid method  
was made and that it was about two  
and a half times the normal"

For references see text

TABLE 1 — (Continued)

Case No and Author*	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
51 — Voelcker	Case mentioned by Weber as having been observed by Dr A F Voelcker but which had not yet been published. It is assumed from Weber's reference that this was a typical case, but no details were given.		See "History"	Apparently no detailed report has been made of this case
52 — Cassner and Bam- berger	Male, aged 39. Of a nervous family. It is worked hard and had much trouble. Is hypochondriacal, feared spinal and brain disease.	Cyanosed. Spleen enlarged. Liver moderately enlarged. Blood vessels dilated. Temperature always below 98.6 F. No albumin in urine.	Red cells 8,500,000 to 9,600,000. Hemoglobin 130.160. White cells 9,760. A month later red cells 6,150,000.	Patient left sanitarium improved and took up his work. No further examinations.
53 — Schupfer	Male, aged 42. Enlarged spleen removed for supposed Banti's disease and progress followed for 3 years. Patient improved in general health and liver, enlarged before operation, returned to normal size, but polycythemia and chronic cyanosis gradually developed.	Chronic cyanosis. Spleen enlarged. Transitory enlargement of liver.	Red cells (on two counts before operation) 2,899,000 to 4,920,000. Three years after operation red cells 6,270,000.	
54 — Mc Quitty	Male, aged 46, watchman, formerly policeman. High colored for 20 years. Illness began in June, 1905, with pain in left hypochondrium. Admitted July, 1907, complaining of numbness and lividity of left hand, weakness, loss of flesh and swelling in abdomen. In September, 1907, attack of vomiting and diarrhea with passage of a large amount of blood. Was weak for a few days afterwards but pain between shoulders, headache and giddiness disappeared and did not return while under observation.	Face, tongue and mucous membrane livid red, both hands bluish red. Spleen 4 inches below costal margin. Liver the same. Lungs negative. Heart negative at first but while under observation developed a slight systolic murmur and accentuated aortic second sound. Capillaries dilated, marked tortuosity and thickening. Left radial artery and visible pulsation large arteries. Pulse of increased tension. Optic fundi normal. Knee jerks minus. Urine contains albumin.	Red cells 9,400,000. Hemoglobin 162. White cells, 12,100. Polys 80 per cent, L Eosino 6 per cent, Lymph 3 per cent, S lymph 9 per cent, Transits 2 per cent. Color index 0.91.	In January, 1908, was much less cyanotic and heart had developed a murmur at apex, liver and spleen enlarged. Treatment potassium citrate given four times daily for ten weeks. During its administration numbness and lividity of the left hand gradually disappeared and the patient felt better, with no recurrence of the vomiting and diarrhea.

55 —  
Cautley

Male, aged 47  
Complains of tender  
swelling in splenic area

Face varied from deep red to cyanotic  
Spleen enlarged Albuminuria present

Red cells 7,500,000 to 10,000,000  
Blood extremely viscid

Death from cerebral hemorrhage  
Autopsy Spleen firmly adherent to surrounding structures and contained two infarcts Soft splenic bands divided into lobules by fibrous bands Cardiac hypertrophy Granular kidneys Bone marrow of long bones red Cautley thinks condition a result of local thrombosis of extremely viscid blood and that microscopic examination of marrow of organs did not afford any indication as to etiology  
Venesection nine times in two years, in amounts from 20 to 25 ounces, with marked relief on each occasion Patient was discharged in three months in much the same condition as when admitted to hospital

56 —  
Chambers

Female, aged 65  
Illness began in 1899 with pains in abdomen, dyspepsia and palpitation following severe strain in lifting Has had frequent attacks of dyspnea and cyanosis Venesection nine times in two years with marked relief on each occasion Admitted Nov 15, 1906, on account of pain, dyspepsia and palpitation pleurisy for a year before he came under observation

Plethoric looking but not markedly cyanotic Spleen distinctly enlarged and tender Liver just palpable below costal arch Recent bronchial catarrh Heart enlarged to right Pulse 86, full and regular Respiration 24 Temperature subnormal Patient well nourished

Red cells 6,660,000 Later 7,800,000 Had been as high as 12,000,000 at one time Hemoglobin at present 105

57 —  
Munzer

Cyanosis of face Spleen greatly enlarged Liver somewhat enlarged Urine contains much albumin

Red cells 7,000,000 Hemo-  
globin, Sahli, 135, Fleischl, 140 White cells 20,000 Color index 1.00

Treatment dietetic proved Patient left im-

\*For references see text

TABLE 1 — (Continued)

Case No and Author *	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
58 — Chace	Female, aged 17, school girl Except for measles in childhood, health has always been good Has never menstruated Three years ago confined to house with severe cough Since then palpitation, hoarseness, general weakness, blueness of lips and fingers and irritable disposition Three months ago fainting spell, preceded by distinct aura consisting of groaning and twitching of muscles of forehead Consciousness lost for about five minutes and on awakening found bed clothes saturated with blood from nose During following three months four similar attacks accompanied by aura and severe epistaxis On admission, Aug 19, 1967, complained of above symptoms and of headache and distress in epigastrium	Skin very dusky, lips, tongue, gums and conjunctivæ blue Spleen one and a half inches below costal margin Lungs normal Heart forcible and accelerated Dilated veins and venules, marked pulsation of carotids, blood-pressure 120 Skin slightly pigmented Decayed teeth Fingers slightly clubbed and nails incurvated Atrophied uterus Urine showed slight trace of albumin and occasional traces of indican	Red cells 5,917,500 to 7,568,000 Hemoglobin 110-112 White cells 4,000 to 6,250 Polys 64 to 76 per cent, Lymph 24 to 31 per cent, Eosino 0 to 1 per cent, Transit 0 to 4 per cent	No improvement in hospital Potassium iodid, oxygen inhalations, and high colonic irrigations all without much benefit She felt better after withdrawal 7½ ounces venous blood but this procedure discontinued account of weakened condition Patient discharged Sept 24, 1907 Most severe symptoms were headache, indefinite abdominal pains, occasional palpitation and malaise Had one slight convulsion with rather severe epistaxis Three months after leaving hospital she wrote that she had become quite weak and averaged two fainting spells weekly, followed by severe headache Also attacks of numbness in left leg and was growing progressively weaker and more cyanosed Chace calls attention to this patient being the youngest reported (since then Sandesky has reported a patient of the same age—Case 67) Under treatment with bromids and sodium iodid, and later sajodin, chacea decreased, patient improved and left hospital
59 — Baishachzi	Female, aged 59 Three months ago, after some excitement, noticed twitching in right hand, which soon extended to whole body with the general appearance of chorea	Cyanosis of face Liver enlarged Spleen enlarged	Red cells 10,900,000 Hemoglobin, Fleischl, 135 White cells 7,000 Later red cells 9,750,000, hemoglobin 120 and white cells 13,000 Color index 0.62	
60 — Miller	Male, aged 39 Began to suffer at Christmas, 1906, from dyspnea, pains in chest and legs and occasional bleeding from gums No history of syphilis	Giant cyanosis of face, lips, fingers and toes Spleen enlarged and hard Heart normally located, impulse powerful, first sound labored and second sound accentuated at aortic area Blood pressure 124 Legs swollen No clubbing Urine shows trace of albumin	Red cells 11,300,000 Hemoglobin 180 White cells 15,300 Polys 81 per cent, lympho 12 per cent, no abnormal cells, coagulation time 6 minutes at 98.6 F Viscosity 16 Oxygen capacity 1,480 cc Blood vol 4,765 cc Color index 0.8	

61 —

Thompson

Male, aged 37, employed in gas works  
Syphilis 38 years ago, employed in  
gas works during the past three  
years. Has been gradually becoming  
blue and complains of headache  
and weakness. At one time showed  
signs of mental disturbance.

62 —

Combs-  
Smith

Male, aged 32. Does not use alcohol  
nor tobacco. Denies venereal disease.  
About a year ago first had  
headache and face began to show  
cyanosis. Six months later vertigo

Cyanosed. Spleen much enlarged. Liver  
just palpable. Arterial, venous and  
capillary blood pressure normal.

Cyanosis of face, lips, etc. Spleen  
much enlarged. Liver enlarged.  
Veins of forehead and abdomen distended.  
Fundus oculi shows marked  
venous congestion. Temperature  
about 99.4 F.

Face, and especially nose and cheeks,  
purplish. On arms, legs and abdomen  
purplish blotches size of silver  
dollar to size of palm. Tongue  
clean but cyanotic. Spleen 3 inches  
below umbilicus, is smooth, hard  
and not tender. Liver extends to  
level of umbilicus, is smooth, hard  
and not tender. Lungs normal,  
inspirations 20 to 22. Heart shows  
slight accentuation second sound,  
pulse 85 to 95, hard and compressible  
with difficulty. Superficial veins  
much distended and dark. Ophthalmoscope  
shows enlargement and tortuosity  
of retinal veins, pupils react promptly  
to light. Reflexes normal. Skin thin,  
shriveled and inelastic. Large cystic  
glandular enlargement of thyroid.  
Hippocratic nails typical. Account of  
weakness. Temperature always normal  
or slightly subnormal. Percussion along  
shin bones elicits some tenderness. Urine  
shows trace of albumin, urea 3 per cent,  
specific gravity 1.010. Height 5 feet  
5 inches, weight 115 pounds.

63 —

Seufert

Female, aged 61, German, housewife.  
Mother died of heart disease at 60,  
one brother of phthisis at 50, two  
sisters at 60, unknown cause. Usual  
disease of childhood. Menstruated  
ages 14 to 41. Never pregnant, no  
uterine or ovarian disease. After  
menopause developed cystic goiter  
which grew up to time of death.  
Six years ago headache, giddiness  
and weakness. Five and half years  
ago swellings both sides of abdomen.  
Since beginning of this trouble  
sweating, indigestion without vomiting,  
and spots over body which are  
cold in warm weather and purple in  
limbs, mucous membranes also  
being purplish blue. Mucous diarrhea  
for past year.

Red cells varied from 10,000,000  
to 13,000,000. Hemoglobin 140.  
Blood pigment normal. Total volume  
blood 2½ to 3 times the normal.  
Oxygen capacity 2½ times normal.

Red cells 6,850,000 to 8,500,000.  
Hemoglobin 95-120. White cells  
7,000 to 12,500. Polys 69-87 per cent,  
lymph 6-12 per cent, mononuc  
5-15 per cent, Eosinophils 1-9 per  
cent.

Red cells 15,500,000. Hemoglobin 180.  
White cells 14,000. Neutrophils leukocytes  
53 per cent. Eosinophilic leukocytes  
4 per cent. Basophilic leukocytes  
2.5 per cent, mononuc leukocytes  
3 per cent, lymph 23 per cent, small  
lymph 14.5 per cent, large lymph  
14.5 per cent, coagulation time one  
minute. Red cells normal in size and  
shape with an occasional normoblast.  
Blood very dark and viscous. Spread on  
slide with great difficulty. Color index 0.58.

Died of tuberculosis. No autopsy.

Died in March, 1909. Treatment in  
this and in the following case had  
little, if any, influence on the course  
of the disease. Arsenic, quinin and  
the x-ray were faithfully tried but  
without any result. Inhalations of  
oxygen gave temporary relief for  
at least twenty-four hours at a time.  
Removal of 250 cc of blood in this  
case gave only transient relief for  
not over forty-eight hours.

\*For references see text

TABLE 1 — (Continued)

Case No and Author*	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
64 — Seufert	Female, aged 43, Russian Jewess, housewife. Mother died at 51, hav- ing been bed ridden each winter for twenty years with cough and hemop- tyses. One sister died at 48 of kid- ney disease. Menstrues at 6, normal menstruation 14 to 42. Married at 20, five children and four miscar- riages. Health perfect up to 17 when began to complain of dizziness and nausea, followed by headache and severe pain in fingers and toes with no relief night or day. Six years ago miscarriage and severe hemorrhage with prompt relief in fingers. Came under observation in 1906 account of weakness, dizzi- ness and inability to stoop account of lump in left side. Intense thirst since the beginning of disease. Sleeps well but cannot lie on left side.	Face, and especially lips, nose and cheeks, purple, conjunctivæ, tongue and buccal mucosa very purple, purple patches over body, especially arms and legs. Spleen extends to ilac crest. Liver, at first normal, now greatly enlarged and both or- gans smooth, hard and not tender. Varicose veins, especially of left leg, but no edema. Nails markedly Hippocratic. No glandular enlarge- ment. Skin flabby and muscles atrophic. Pulse 85 to 95. Reflexes normal. Pupils equal and respond promptly to light, ophthalmoscope shows some tortuosity and enlarge- ment of veins. Uterus prolapsed. Urine shows urea 2.5, uric acid greatly increased and diazo reaction always present, specific gravity 1.020.	Red cells 15,000,000. Hemo- globin 170. White cells 12,- 500. Neut. leuko 73 per cent, Eosin leuko 2 per cent, Baso leuko 1.8 per cent, Mononuc. leuko 3.2 per cent, Small lymph 4 per cent, Large lymph 16 per cent. Coagulation time 1 minute. Occasional nor- moblasts and megaloblasts. Color dark red and coagu- lated so quickly it was dif- ficult to make blood counts. Color index 0.57.	Splenic enlargement was first noticed by patient after birth of last child nine months previous to time when she came under observation. In the two and a half years during which she was under observation all of her symptoms have become more severe, the general weakness more pro- nounced, the spleen has varied very little in size and she has lost 50 pounds in weight. As to treatment, see preceding case.
65 — Drum- mond	Male, aged 44, miner. Admitted to hospital in August, 1908, with a history of headaches and giddiness over a period of ten years.	Lips deep blue, tongue and palate brilliant dark scarlet, legs and hands red. Spleen enlarged. Heart not enlarged. Pulse full. Blood pressure 120.	Red cells 12,000,000. Hemo- globin 170. White cells 12,- 000, mostly polymorphonu- cleus. Color index 0.71.	After a short time in hospital patient returned to work, but symptoms be- came aggravated with vomiting and occasional blood in urine.

66 — Snyder	Male, aged 33, soldier typhoid fever in 1904 exhaustion after slight physical exertion, also of giddiness and faintness, pain in left hypochondrium and cough	Cyanosis of face enlarged Spleen greatly enlarged Temperature normal Arteries tortuous Urine shows trace of albumin, sp gr 1.010	Red cells 10,600,000 Hemoglobin 120-160 White cells 18,000 to 23,000 Polys 80-83 per cent Lymphocytes 14-18 per cent Large mononuc 0-2 per cent Eosin 0-3 per cent	Hemo- globin 105 White cells about 71 per cent Mononuc about 28 per cent Eosinophils 1 per cent	Treatment arsenic and iodids not mentioned	Results
67 — Sandsky	Female, aged 17 Complains of cough, expectoration, etc	Cyanosis placed Spleen enlarged Heart dis-	Red cells 6,380,000 Hemo- globin 105 White cells 8,700 Polys about 71 per cent Mononuc about 28 per cent Eosinophils 1 per cent			
68 — Kuttner	Female, aged 48, single tary taint Sickly for years past four years bluish red discoloration of skin, pain in joints, headache, dizziness, weakness, palpitation, dyspnea and disturbances of digestion	Marked cyanosis of skin and mucous membranes Spleen three finger breadths below costal margin Lungs and heart practically normal Varicose veins of legs Blood-pressure 145 Eyes hyperemic Urine practically normal	Red cells 8,000,000 to 10,000,000 Hemoglobin 150-240 White cells 6,600 to 8,500 Polys 75 per cent Lymph 16 per cent eosin 5 per cent myeloc 4 per cent Sp gr 1.060 to 1.076 Viscosity 20 to 40			
69 — Jump	Dr H D Jump has kindly given permission to mention the case of a man who has been under his observation for some time and who was presented by him before the West Branch of the Philadelphia County Medical Society in April, 1912 Dr Jump will report this case elsewhere.	Marked dark reddish discoloration of face, upper part of chest and hands Spleen markedly enlarged	Marked increase in red cells			

\*For references see text



TABLE 2 (CLASS B) — CASES WITH CYANOSIS AND SPLENOMEGALY AND WITH A SYSTOLIC BLOOD PRESSURE EXCEEDING 150

TABLE 2 (CLASS B) —CASES WITH CYANOSIS AND SPLENOMEGALY AND WITH A DISCREPANCY BETWEEN THE HEMOGLOBIN AND HEMATOCRIT					
Case No and Author*	History	Examination	Blood Examination		Outcome, Treatment, Autopsy and Remarks
			Red cells	Hemo- globin	
70 — Osler	Male, aged 44, physician Habits good No previous illness For five years fullness of head, giddiness, cyanosis, and constipation	Marked general cyanosis Moderately enlarged spleen (edge palpable) Liver not enlarged Lungs normal Heart slightly enlarged but no mur- murs Blood pressure 170 to 200 Conjunctiva injected Urine shows trace of albumin and a few hyaline and granular casts	Red cells 9,952,000 globin 120 4,000 Color index 0.6	White cells	
71 — Weber and Watson	Male, aged 58, Dutchman Always subject to indigestion, constipation, headache and insomnia For past six years liable to blueness of nose and extremities Hematemesis five years ago Fractured rib three months ago Signs of insanity de- veloped shortly after and removed to asylum	Marked cyanosis of face and extrem- ities Spleen enlarged Liver nor- mal Lungs slightly emphysema- tous Heart normal Pulse, high ten- sion Blood-pressure 140 to 170 Urine shows cloud of albumin, ex- cess of urobilin but no casts	Red cells 9,000,000 to 11,000,- 000 Hemoglobin 170 White cells 7,500 to 12,000 Differ- ential normal No abnormal red cells Sp gr over 1.066		Patient died soon after in syncope with increased cyanosis Autopsy Spleen 23 ounces, scaried with old infarct, otherwise substance normal Liver normal Lungs engorged, mod- erately emphysematous and con- tained few small infarcts Left ven- tricle hypertrophied, old vegetation aortic valve and slight thickening mitral Stomach congested and round ulcer near pylorus Marrow of long bones red, consisting chiefly of normoblasts and myelocytes Weber considers changes insufficient to account for symptoms
72 — Parkes Weber	Female, aged 37, Roumanian Jewess Inflammation of womb and swelling of left extremity seven years ago after birth of second child For two or three years headache, giddiness and prostration Two years ago acute erythromelalgia of left foot Year ago polycythemia and enlarge- ment of spleen	No marked cyanosis but fingers and toes rather livid and tongue bluish Spleen extends 1 inch below costal margin Liver not enlarged Lungs and heart normal Cutaneous ves- sels overfilled High pulse tension Blood pressure 160 Vessels of fun- dus oculi engorged and tortuous Urine about normal	Red cells 8,000,000 to nearly 11,000,000 Hemoglobin 145- 180 White cells 4,000 to 9,000 Polys moderately in- creased Sp gr 1.072 1.078 Nucleated reds present 10- tal volume and viscosity greatly increased Crys- copy and resistance hemol- ysis about normal		Condition about the same two years later Some improvement occurred but polycythemia persisted Total volume blood 5,600 to 6,000 cc (normal individual estimated to possess 4.6 cc per 100 gm of body weight) See text as to blood-vis- cosity

71—

Ronald-  
son

Female, aged 62. Has had six children, one dying of phthisis and one of heart disease. Has always been of present color. Twenty years ago rheumatic pains confined her to bed for a short time, does not think she had fever. Constipated for three years. Lately tired and dyspnoeic on exertion for two years. Slight vertigo on stooping.

Face dusky purple, numerous dilated venules over cheeks and nose, rest of body redder and hands almost rose tint, mucous membranes livid, dilated capillary points over trunk. Spleen 2 inches below costal margin. Liver slightly enlarged. Lungs normal. Heart somewhat enlarged, first sound sometimes reduplicated, arteries thick and tortuous. Blood-pressure 180 to 190. Urine shows faint trace of albumin and a few hyaline casts, much urobilin and urochrome present. Cyanosis of face and extremities. Spleen enlarged. Liver enlarged. Lungs normal. Heart hypertrophied. Blood-pressure 180. Conjunctivae injected. Veins distended. Urine shows albumin but no casts.

Red cells 8,152,000 to 9,175,000. Hemoglobin 130-145. Polys 77 per cent. Lympho 23 per cent. Blood very dark and viscid. Glycogen reaction distinct but not marked.

71—

Bence

Male, aged 13. Ague at 12. Pneumonia at 13. Cough and dyspnoea for some years. For last six years marked cyanosis face and hands, attacks of headache, giddiness and vomiting and inability to bleed from gums and nose.

75—

Saund  
by

Male, age not stated. Two years ago swelling of legs following influenza. At that time was florid with a blue tongue. No enlargement of spleen and no blood count, case being regarded as thrombosis inferior vena cava. In a week, after rest in bed, swelling of legs disappeared, but they remained painful. Although better, was never able to do same work. A year ago readmitted for return of leg swelling and for swelling of abdomen lately noticed. Some dyspnoea.

Florid. Tongue blue. Spleen palpable. Liver half way to umbilicus. Heart somewhat enlarged. Veins distended. Blood-pressure 170 to 180. Edema walls of chest and abdomen. Legs swollen. Knee jerks absent. Retinal veins full. Dermatographia present. Urine shows albumin and much indican.

Red cells about 11,000,000. Hemoglobin 180. White cells 11,000. Moderate relative increase of polymorphonuclear cosmophils. Color index 0.81.

Red cells 7,144,000 to 9,200,000. Hemoglobin 140-190. Differential normal. Viscosity about twice normal (94). No abnormal reds. Sp. gr. 1.075. Coagulation time 8 to 10½ minutes.

Treatment. Aiseric, non-adrenalin chlorid, quinin, diuretin and bleeding up to twelve ounces with temporary relief. Colon has been systematically irrigated with large amounts (5 to 6 pints) of water, which for some time contained 5 gr. alpha naphthol to the quart, all without appreciable relief. Erythrol tetranitrite without much benefit (blood somewhat reduced in pressure). Also tried vinegar (old idea that it thins the blood) with some apparent effect on the polycythemia.

\*For references see text

TABLE 2 — (Continued.)					
Case No and Author*	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks	
76 — Senator	Male, aged 58, Russian Pole, merchant. Healthy all his life but for years has had red face. Two years ago weakness, loss of appetite and vertigo, was then markedly cyanotic with enlarged liver and spleen, nephritis and polycythemia. Three months ago severe epistaxis, after which felt better. Two weeks later paralysis of right hand and right lower facial nerve region, as well as aphasic disturbances.	Mucous membranes dark blue, at one time markedly cyanotic. Spleen and liver enlarged. Heart normal. High arterial tension, blood pressure 155 to 160. Slight paralysis extremities right side. Slight motor aphasia. Urine 1,400 to 1,700 cc, sp gr, 1.014 to 1.017, albumin 0.4 to 0.7.	Two years ago red cells 8,710,000, white cells 18,480. Last year red cells 6,950,000, white cells 12,500, hemoglobin 145, color index 1.05. Polys 86.4 per cent, Mononuc 2.3 per cent, Lymph 5.8 per cent, Eosin 2.9 per cent, Mast cells 2 per cent, Myeloc 0.7 per cent.	Treatment two years ago dietetic and hygienic. Three months ago injections of sodium cacodylate (0.05 to 0.075 daily), spleen much reduced but blood unaffected. K I produced increase of redness and conjunctivitis and was given up. Faradization of spleen, quinin, albumin poor diet, venesection and leeches all without much effect.	
77 — Nicola	Male, aged 51, married, home Oklahoma. Well during early life. Positively denies venereal taint. For three years weekly attacks of headache, face becoming red although extremities cold and clammy. During past six months several severe attacks of headache, requiring hypodermics, and accompanied by giddiness, flashes of light, extreme photophobia, cyanosis of face, neck and fingers, ulcers and considerable hemorrhage from gums and pharynx. Feels "groggy" all the time and mind is cloudy. Bowels obstinately constipated. No dyspnea.	Face and neck dark red, hands less so and unexposed surfaces normal color, nose, ears, lips, tongue and mucous membranes all bluish red. Spleen 1 inch below costal margin. Lungs and heart normal. Blood pressure 153. Conjunctivae injected, veins of fundus oculi blue, dilated and tortuous. No blood or parasites in feces. Urine shows considerable indican and uric acid crystals and a few hyaline casts.	Red cells 6,000,000 to 8,000,000. Hemoglobin, Dare, 120. White cells two and a half times normal. Polys 84.5 per cent, S lymph 6.8 per cent, Myeloc 1.6 per cent. Megaloblasts three times in eight counts. Two normoblasts in eight counts. Color index 0.75 to 1.00.	Three attacks in hospital, first severe headache with marked cyanosis and capillary hemorrhage from mouth and pharynx, second pain around heart and down left arm with increased cyanosis, and, third, pain and tenderness in calf of right leg and distressing pruritus after bathing, affecting legs especially. Under symptomatic treatment, tonics and eliminatives, patient improved, but cyanosis almost disappeared, but polycythemia not affected by treatment nor by x-ray or K I.	
78 — Parker and Slocum	Male, aged 43, American, laborer. Asthmatic attacks since 30 years ago. Attack of "asthma" with unconsciousness. Four years ago noticed blueness face, hands and feet with variable swelling. Four months ago, blueness, which had disappeared, became marked, especially when working or excited, and palpitation, dyspnea, severe frontal headache, dizziness and prominence of the eyes became marked.	Startling general cyanosis, especially of nose, lips, chin and ears, hands and feet moderately blue, palate and tongue deep purple. Spleen enlarged (see "Remarks"). Liver just palpable. Lungs emphysematous, dyspnea on exertion. Heart negative at first (see "Remarks"). Radials moderately sclerosed, pulse fuller left than right, blood pressure left 156, right 146. Eyes prominent (see "Remarks"). Conjunctive suffused. Urine shows moderate albuminuria and many granular casts and cylindroids. X-ray examination see "Remarks."	Red cells 6,540,000. Hemoglobin 100 plus. White cells 6,500. Polys 67.6 per cent, small lymph 14.8 per cent, large lymph 3.8 per cent, eosinophils 3.8, mast cells 1.6 per cent, degenerated red cells 8.4 per cent. Later red cells 7,400,000. Sp gr 1.062. Coagulation time less than one minute. See also "Remarks."	Temporary improvement, patient left hospital in 1908. Fluoroscope and radiogram revealed non-pulsating shadow in mediastinum thought to be a tumor. Eyes showed more or less blurring of vision and occasional diplopia, vision 0/D 20/100, 0/S 20/50. Veins of fundus markedly tortuous and dilated. Retina deeper red than normal and edematous. Two years later heart enormously dilated, spleen just palpable, lungs emphysematous, red cells 7,200,000, hemoglobin 120, white cells 10,320 and blood pressure 136.	

74 -  
Pituitary  
and  
Gonadotropin

Male, aged 31, American, Farmer  
Always well up to one year ago  
when began to have headache, numb-  
ness of fingers, tinnitus aurium, numb-  
ness of fingers, tinnitus aurium, and  
ophthalmological clinic complaining  
of severe frontal headache, blurring  
of vision, diplopia and extreme  
weakness. Marked dyspnea

Enlarged Spleen 1 inch below costal  
margin Liver not enlarged Lungs  
negative Heart moderately en-  
larged Blood-pressure 165 Slight  
general glandular enlargement  
Eyes vision O/D 6/7.5, O/S 6/9,  
return hyperemic, veins much en-  
gorged, tortuous and dark in color

Red cells 3,000,000 to 9,000,-  
000 Hemoglobin 110 White  
cells 14,000 Polys 87 per  
cent, S lymph 22 per  
cent, L lymph 32 per  
cent, Eosin and mononuc  
16 per cent, myelo 14 per  
cent, mast cells 08 per  
cent, degenerated cells 38  
per cent One normoblast  
and one megaloblast Some  
irregularity in red cells

80 -  
Umney

Female, aged 31, married Family his-  
tory of nervousness One brother  
died from phthisis As a girl suf-  
fered from anemia Soon after mar-  
riage noticed bluish color to com-  
plexion, which was greatly intensi-  
fied in cold weather General health,  
however, was good Menses irregu-  
lar since miscarriage in August,  
1902 Came under observation in  
October, 1905, on account of rather  
profuse menstruation after absence  
of four months When seen by Um-  
ney this had ceased but she had  
hematuria lasting a few days and  
followed by a permanent albumin-  
uria

Whole body remarkable color, cheeks,  
nose, lips, ears and fingers bluish  
red and skin of chest, back and ab-  
domen uniformly red Palms of  
hands also quite red Spleen three  
or four finger breadths below ribs,  
not tender Liver not felt Lungs  
and heart normal Radial arteries  
considerably thickened, pulse regu-  
lar and tense Blood-pressure 170  
(see "Remarks") Tiny venules  
noticed on cheeks No clubbing of  
fingers Conjunctivae injected  
Kidneys somewhat movable and  
somewhat enlarged Urine shows  
considerable albumin and a few  
granular casts and red cells

Male, aged 50 Case presented before  
the St. Louis Medical Society, show-  
ing polycythemia, splenomegaly and  
marked cyanosis of the face, hands  
and feet

Face mottled, deep brownish appear-  
ance with a tinge of purple, most  
marked about the nose On reclin-  
ing this red and purple discolora-  
tion more marked Hands and feet,  
mouth and rectum also highly cyan-  
otic Spleen three fingers breadths  
below costal margin and hard and  
sensitive (see "Remarks") Lungs  
normal except slight accentuation  
of breath sounds Blood pressure  
155 Blood in stools and stomach  
contents Active lesions of  
present on forehead and back  
Very red and cyanosed Spleen shows  
pericussion enlargement Liver not  
enlarged Heart not enlarged Blood-  
pressure 240  
Bluish red color Spleen shows percus-  
sion enlargement Liver not en-  
larged Heart slight enlargement to  
the left Blood-pressure 185 to 200

Male, aged 50 For 18 years palpi-  
tation, tinnitus aurium, pain in  
throat, headache and vertigo

Male, aged 58 For many years nose  
bleed, congestion of the head, ver-  
tigo and insomnia

82 -  
Stache  
lin

83 -  
Stache  
lin

\*For references see text

Patient led ordinary life without vari-  
ation symptoms or further attacks  
of hemorrhage for two years Men-  
struation occurred only at long in-  
tervals and always scanty Treat-  
ment directed to reestablishing men-  
struation had no effect on cyanosis,  
spleen or condition of blood Just  
before Christmas, 1907, she devel-  
oped chorea and thrombosis left  
jugular and other veins Blood pres-  
sure was 170 arterial and 40 ven-  
ous Patient died March 19, 1908,  
after developing edema lower half  
of body No autopsy At time of  
death main veins in all four limbs  
and both sides of neck were plugged  
Blood from different parts body shows  
practically same findings Just be-  
low splenic mass is a palpable mass  
of much the same consistency, ap-  
parently separated from the spleen  
and measuring 11 by 6 cm and  
which is either a part of spleen or  
possibly a supernumerary spleen  
Myer suggests that lues be borne in  
mind as a possible etiologic factor  
and proposes instituting active an-  
tiletic treatment

Red cells 12,880,000 Hemo-  
globin 120 White cells 20,  
600 Polys 92 per cent,  
lymph 3 per cent, large  
mono 23 per cent, eosin  
13 per cent, baso 13 per  
cent Coag time 7 1/2 to 8  
minutes Blood flows slowly,  
is dark and viscid Color  
index 0.46

Red cells 5,000,000 to 6,200,  
000 Hemoglobin 147-167

Red cells 6,200,000 Hemo-  
globin 163 Color index

TABLE 3 (CLASS C) —CASES WITH EITHER CYANOSIS OR SPLENOMEGALY ABSENT AND IN WHICH BLOOD-PRESSURE DOES NOT EXCEED 150

Case No and Author*	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
84—Moutard Martin and Lefas	Female, aged 49 Typhoid in childhood For past year pain and swelling in left hypochondrium	No cyanosis Spleen enormously enlarged Liver slightly enlarged Lungs, heart and urine normal	Red cells 8,200,000 cells 31,400	White Died soon after with vomiting and fetid diarrhea Autopsy Spleen 1,750 gm and showed scattered nodules apparently tuberculous Liver 2,000 gm Lungs and heart normal
85 — Cabot	Female, aged 46, masseuse Six years ago had fit with unconsciousness and thick speech Four years later mental and muscular weakness, face purple and eyes injected	Cyanosis of face and tongue splenic enlargement reported Heart normal Urine showed traces of albumin and a few hyaline casts	Red cells 10,460,000 globin 150 White cells 20,000 Color index 0.7	Hemo- Died within a few months of middle meningeal hemorrhage Autopsy revealed nothing in addition except great congestion of all the viscera
86 — Hall	Female, aged 61, Jewess, born in Germany Dyspnea and palpitation since menopause Sleeps well, appetite good No pain, always thirsty Mother of six children Patient's son thinks that patient's mother presented a similar discoloration of the lips and face and enlarged veins during latter part of her life The patient's children are still under middle age and none has shown any symptom of this condition	Strutting cyanosis, lips and tongue of the color of a ripe Concord grape, slightly less marked on hands and still less on trunk and lower extremities Spleen and liver negative Lungs slightly edematous, marked dyspnea on slight exertion Heart slightly enlarged Arteries moderately atheromatous, veins distended and tortuous, pulse of increased tension Lips tremulous Eyes see "Remarks." Urine contains albumin and casts, sp gr 1.012	Red cells 10,000,000 globin 170 200 White cells 6,500	Patient continued in same state of health and without marked alteration in vision from June, 1903, to June, 1904, when she died after a few hours illness with symptoms of acute cardiac failure No autopsy Jackson (in Ophthalmology, Milwaukee, 1907) shows two plates of the eye grounds in this case and goes fully into the eye condition over a period of three years The vision steadily decreased, there was low myopia with slight rotary nystagmus and epiphora Pupils became unequal and light reaction was disturbed There was great dilatation of left central retinal vein where it disappeared in nerve head Jackson says "In June, 1903, the sinus of left nerve is probably twice as large as a year ago and differs from anything I have seen before"

87—

Colony

Male, aged 32, Hebrew, peddler. After being under observation for four years on account of progressive muscular atrophy, patient developed cyanosis of extremities.

88—

unk

Male, aged 35. Typhoid ten years ago for two years headache, constipation and pain in right hypochondrium. A year ago liver found to be enlarged.

Cyanosis of extremities. Spleen not enlarged. Liver not enlarged. Lungs, heart and urine normal.

Red cells 8,400,000  
globin over 100  
normal White cells

Red cells 8,000,000, falling to 5,160,000 before death. White cells 10,000. A very few nucleated reds, erythroblasts and myelocytes.

No cyanosis. Spleen reached to iliac spine. Liver 2 inches below costal margin. Slight bronchitis and emphysema. Heart about normal. Urine normal except excess of urobilin and a little bilirubin. Jaundice and emaciation.

Patient became more jaundiced and died soon after with hemorrhage from nose, stomach and intestine. Autopsy: Spleen firm, weighing 930 gm., and bound by adhesions to liver. Hypertrophy and cirrhosis of liver with regenerative changes (multiple adenomata). Had been long bones dark red and of faulty firm consistence.

Patient died on the second day. Autopsy: Liver and spleen small and blood. Lungs contain much bronchial catarrh and bronchiectasis. Dilatation of right heart. Numerous hemorrhagic erosions of stomach and duodenum. Ulcer of leg. Universal mechanical hyperemia. Bilateral hydrothorax. Edema of lower extremities. Old tuberculosis. Chronic arthritis deformans. Later the red cells from ear were 10,426,000 and at same time from finger were 9,700,000.

89—

unk

Female, aged 47

Cyanosis present. Spleen not enlarged. Liver not enlarged. Lungs emphysematous, chronic bronchial catarrh and bronchiectasis. Heart rapid and arrhythmic. Patient dyspneic. Abdominal wall edematous. Urine shows trace of albumin, urobilin and indican.

Red cells 5,700,000 to 6,215,000. Hemoglobin 154-168. White cells 7,500 to 9,400. Numerous normoblasts present in stained specimen.

90—

unk

Male, aged 36

Has suffered for a year or two from headache, giddiness and dyspepsia. A year ago slightly enlarged but the liver normal. Two months ago spleen and liver greatly enlarged.

No cyanosis but mucous membranes of mouth very red. Spleen reached to iliac crest. Liver enormous. Lungs normal. Heart apex beat displaced upwards to the fourth interspace. Urine shows albumin, casts, urobilin and excess of indican.

Red cells 10,107,000. Hemoglobin 185. White cells 34,000. Polys rel increased. Lymph 4 per cent, large mononuc 48 per cent, eosin 68 per cent, mast cells 14 per cent. One myelocyte and one normoblast. Blood dark and viscid. Color index 0.91.

\*For references see text

TABLE 3 — (Continued)

Case No and Author*	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
91 — Zaudy	Female, aged 27, single Gastric fever eight years ago At about same time the spleen enlarged Menorrhagia un- til two years ago Severe dyspnea for some weeks	No cyanosis but very bright red com- plexion Spleen reaches to umbili- cus Liver not enlarged Lungs, heart and urine normal	Red cells 9,400,000 Hemo- globin over 100 (limit of scale) White cells 18,000 No abnormal red cells	Dyspnea soon disappeared and she ceased to remain under observation
92 — Wein- traud	Male, aged 36 Malaria at 19 Always asthmatic but better since operation on nose at 26 Two years ago well- marked cyanosis of face and extrem- ities, spleen, liver and heart en- larged, lungs somewhat emphysema- tous and urine showed albumin Fif- teen months ago phlebitis of left leg One year ago spleen and liver no longer palpable	Face purple Spleen no longer palp- able Liver 2½ inches below costal margin No dyspnea Blood-pressure 110 Conjunctivæ injected Urine shows albumin but no casts	A year ago red cells were over 10,000,000 At present red cells 7,368,000, hemoglobin 170, white cells 9,800 Sp gr 1,066 Color index 1.16	
93 — Axel- Blad	Female, aged 34 Pain in epigastrium and left hypochondrium	Face congested Spleen enlarged	Red cells 11,000,000	Spleen excised and death occurred a few days later Autopsy Showed death to be due to profuse internal hemorrhage Spleen showed some small infarcts and microscopically seemed to show enlargement to be due to simple hyperplasia Liver slightly enlarged and microscopic- ally showed early cirrhotic changes Condition of bone marrow not stated
94 — Reiss- mann	Female, aged 18 For four years lips blue and skin dusky Three years ago had attacks of unconsciousness and vomiting, complained of fre- quent headaches and eyes became prominent Regular menstruation up to five months ago when she de- veloped amenorrhea Two years ago diarrhea and vomiting	Slightly dusky, dry skin, lips blue, mouth and fauces very red Spleen not enlarged Liver dulness slightly increased upwards Breathes a little hurriedly but lungs healthy Heart normal, venous pulsation in neck, pulse 160 Eyes distinctly promi- nent, Von Graefe's sign absent, fine tremor of hands, thyroid not en- larged Optic disks red and veins engorged Temperature 100 Some tenderness right lumbar and sub- costal regions Urine shows trace of albumin, much chromogen and decided acetic acid and trace of ace- tone	Two years ago, red cells 7,- 404,000 Hemoglobin 124 White cells 5,600 Blood very rich color Coag time 30 seconds Viscosity much increased Color index 0.97 After hemoptysis red cells 5,776,000, white cells 12,000 Following March red cells had fallen to 4,- 736,000, white cells 7,000	Vomiting and diarrhea ceased a few days after first observation but gen- eral condition gradually became worse Continuous pyrexia for over a month Operation for liver ab- scess but no pus After operation patient very ill with dulness both lungs and finally coughed up six ounces bright red blood with im- provement Then signs venous ob- struction left leg, persisting for a month In following March patient well and strong but with slight cyanosis, pronounced on exertion At present (two years after severe illness) condition much the same Still slight cyanosis, pronounced on exertion No excess of red cells but blood more viscid than normal

- 95—Geis-  
bock Male, aged 39
- 96—Geis-  
bock Male, aged 50
- 97—Geis-  
bock Male, aged 58
- 98—  
Levi Male, aged 56 Denies venereal disease  
for 25 years slight cough, which  
first noticed bronchitis Ten years ago  
gradually increased blueness face, which  
of nausea, vomiting and uncon-  
sciousness Lately attacks  
Female, aged 21, domestic Four years  
ago complained of dyspnea on exer-  
tion For past year legs swollen  
at intervals and dusky and swollen  
appearance of face and eyelids Has  
had occasional attacks of precordial  
pain and fits after exercise in which  
has lost consciousness and has oc-  
casionally passed urine Blood a  
year ago showed a large excess of  
red cells
- 99—  
Russell Female, aged 42 Cyanosis face and  
extremities for two years Also  
shooting pains in hands and habil-  
ity to bleeding from gums
- 100—  
Bence Female, aged 42 Cyanosis face and  
extremities for two years Also  
shooting pains in hands and habil-  
ity to bleeding from gums
- \*For references see text
- Blood pressure 150
- Heart enlarged and irregular Blood-  
pressure 130 to 140 Urine shows  
albumin and a few casts
- Heart slightly enlarged Blood-pres-  
sure 150
- Cyanosis of face, neck, hands, etc  
Spleen described as "very firm," but  
no mention of enlargement Liver  
enlarged Mucous membranes and  
conjunctivæ injected Patient "a  
strong man" Urine shows some  
albumin
- Face dusky red and swollen, hands  
and feet dark red, mucous mem-  
branes, except lips, not cyanosed,  
numerous scattered pigment spots  
over body Spleen not palpable but  
dulness increased Lungs normal  
Heart somewhat enlarged, short  
systolic murmur at apex, pulsation  
and shock second interspace, pulse  
120, small and low tension, with  
pressure soon fell to about 80, blood-  
fingers 115 Slight clubbing of  
fingers Eyes see "Remarks"  
Urine shows 0.1 per cent albumin,  
1.3 per cent urea and a few hyaline  
and granular casts
- Well marked cyanosis of face and ex-  
tremities Spleen not mentioned  
Liver slightly enlarged Lungs and  
heart normal Conjunctivæ injected  
Urine normal
- Red cells 6,475,000 Hemo-  
globin 124 Color index  
0.97
- Red cells 7,600,000 Hemo-  
globin 150 Color index  
0.99
- Red cells 6,565,000
- Red cells 10,740,000 Hemo-  
globin gr 29 per cent  
(Fleischl) White cells 12,-  
200
- Treatment by arsenic and Roentgen  
rays Patient left somewhat im-  
proved
- Acute symptoms improved with rest  
in bed but polycythemia did not dis-  
appear Eyes conjunctivæ slightly  
edematous with large and tortuous  
vessels Optic disks considerable  
blurring of edges, obviously due to  
edema, right disk veins very much  
enlarged and tortuous, arteries also  
large Outer part of disk showed  
remarkable group small arterioles,  
enlarged vessels scattered about  
retina Near macula small patch  
of pigment, "the result of former  
chorioiditis." Left disk similar in  
lesser degree
- Red cells 6,297,000 to 8,650,-  
000 Hemoglobin over 120  
(limit of scale) White cells  
5,600 to 7,000 Polys 61.4  
to 74 per cent, lymph 19.3  
to 29 per cent, large mono-  
and trans 6.3 to 7.9 per  
cent, eosino 0.2 to 1.9 per  
cent No nucleated reds nor  
abnormal sized or shaped  
red cells A very few mye-  
locytes
- Red cells 8,350,000 Hemo-  
globin greatly increased  
White cells 8,400



TABLE 3 — (Continued)

Case No and Author*	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
101 — Pfeiffer and Behr	Male, aged 37, machinist Denies venereal infection Drinks moder- ately Great exertion in military maneuver "Beating in body sen- sation" From his thirty-fourth year severe nocturnal headaches and cyanosis of face which has gradually increased Later pain under right costal arch, dyspnea and cyanosis of whole body, espe- cially upper half No diagnosis ex- cept catarrh, bronchitis and albu- minuria	Patient "a strong man" Cyanosis of body, more marked in upper half Veins of skin very distinct Spleen apparently not enlarged Liver en- larged Heart normal Conjunc- tivæ injected, moderate choked disk both sides, vision 8/8, retinal veins dilated and tortuous Urine shows albumin and urobilin but no casts Blood pressure slightly increased	Red cells, on nine counts, from April, 1905, to February, 1906, varied from 6,605,000 to 9,100,000 Hemoglobin 110 145 White cells 6,360 to 15,400	Treatment, "as usual without suc- cess" Patient died of cardiac in- sufficiency after being under obser- vation for five years Autopsy Aortic insufficiency, endocarditis aortic valves, some endarteritis Liver indurated from stasis Hyper- emia throughout alimentary tract Small hemorrhage in kidney Hyper- emia of testicles, brain softened Eyes Behr (Klin monats f Augenh, 1911, xlv, 672) goes very fully into eye findings and says this is the first case showing choked disk
102 — Mc Quitty	Female, aged 68 Family tendency to arterial degeneration Ten years ago typhoid Two years later slight congestion of the liver Then healthy up to two years ago when had dial- ysis followed by severe pain in upper abdomen, skin slight yellow, unusual resistance in grill-bladder region, spleen enlarged and urine normal In a fortnight better but weak Continued to have occa- sional attacks of diarrhea and lost 35 pounds Complains of weakness and loss of weight	Cheeks red, tongue very red, scler- otics slightly yellow Spleen three fingers breadths below costal mar- gin Liver finger breadth below costal margin Lungs negative Apex somewhat displaced to left but no murmurs Thyroid slightly enlarged Slight trace of albumin	Red cells 9,500,000 Homo- globin 116 White cells 13,- 000 Polys 46 per cent S lymph 22 per cent L lymph 27 per cent Trans 5 per cent No nucleated cells Viscosity increased Color index 0.61	In the following January patient be- gan to suffer from giddiness and in March was seized with pain in left side of chest with rise of tempera- ture She soon developed crepita- tion and delirium and died on the fourth day McQuitty calls atten- tion to the absence of cyanosis, marked loss of flesh and strength, decrease in polymorphonuclear cells and increase in large lymphocytes and low color index

103 --- 10th	Female, aged 52 married flushed for years Three years ago shivering attacks during next three years and six weeks in bed, followed by thrombosis of vein left leg Leg still swollen, began to have pain in right foot, followed by gangrene of little and third toes Male, aged 67, liberos For seven months had pain in left side, following He has lost weight and complains of weakness	Ice finished umbilicus Spleen extends below liver enlarged and ten der Just heart sound reduplicated	Red cells 7,500,000 Globin 110 White cells 6,500 Color index 0.73	Hemo- Patient improved somewhat under mild doses of arsenic She said that on exertion her skin took on a dark blue color, although no marked cyanosis is seen at present
104 --- Peddy bridge				
105 --- Ambarnd and trees sugar	Female, beyond middle life Had been cyanosed and dyspneic as a child General condition heart disease menopause again became cyanosed and dyspneic	Fluid but not cyanosed Spleen to umbilicus in mid-line, not tender Liver 3 inches below costal margin No dyspnea Heart sounds clear, pulse regular, 78, blood-pressure 140 Marked psoriasis, no edema Retinal veins full but not tortuous, optic disk normal, opacities in lens Knee-jerk normal Urine normal not enlarged Heart somewhat hypertrophied Retinal veins tortuous and engorged with blood	Red cells 8,320,000 Globin 140 White cells 12,000 Differential normal Blood dark and coagulates slowly Color index 0.84	Patient is able to be up and about and has no urgent symptoms
106 --- Herring ham	Female, aged 38 Six years ago was pale and anemic Later high colored with blue nose and subject to attacks of dyspnea and lividity Extreme constipation	Complexion florid, fingers purple Neither spleen nor liver palpable Lungs and heart apparently normal Dyspnea without apparent cause	Red cells on first count 7,800,000, on second count (one month before death) 5,615,000	Diopsy and death Autopsy Spleen not enlarged and to naked eye substance appeared normal Liver enlarged but did not resemble nutmeg scapically Hypertrophy of microtricle, slight thickening of ventricles Chronic interstitial nephritis Bone marrow not examined Soon after examination patient died in one of her attacks of cyanosis and dyspnea Autopsy Spleen enlarged and seemed normal on section Liver congested but not enlarged Lungs emphysematous but not of large type No cardiac disease Bone marrow not examined Birmingham not satisfied that this was case of erythremia but could not explain it otherwise
			Red cells 7,630,000 Globin 120 White cells 8,900 Polys 64 per cent Lymph 25 per cent Basophil 1 per cent Eosin 2 per cent Hyaline methemoglobin No sulphhemoglobin Color index 0.78	

\*For references see text

TABLE 3 — (Continued)

Case No and Author *	History	Examination	Blood Examination	Outcome, Treatment, Autopsy and Remarks
107 — Low and Popper	Admitted into hospital with right hemiplegia of fourteen days' duration	Spleen much enlarged	Red cells 9,300,000 globin above normal White cells 23,000	Death five days after admission Autopsy Spleen engorged, increased reticular tissue, pulp chiefly red blood corpuscles and leukocytes, only remnants Malpighian corpuscles Thrombosis left common carotid and artery left Sylvian fossa with softening left cerebral hemisphere Chronic interstitial nephritis Bone marrow dark red, full of dilated blood vessels, only a few fat vesicles, numerous neutrophilic eosinophils, myelocytes, neutrophils and eosinophilic polymorphonuclears, fewer small and large lymphocytes and erythroblasts (medium quantity)
108 — Hann	Female, aged 18 Well until 13, then bodily development retarded Menstruated twice when fifteen but never since During past two years occasional abdominal pains of uncertain nature Syphilitic taint suspected	No cyanosis Spleen three fingerbreadth below costal margin Liver not enlarged	Red cells 6,000,000 to 7,000,000 Hemoglobin 110 Color index 0.78 to 0.91	In August, 1908, Dr Hann informed Dr Weber that since January (when Weber studied case), under treatment with K I, iodid of iron and occasionally tincture of perchlorid of iron, patient's general condition distinctly improved but splenic enlargement unaltered and polycythemia slightly increased (compare with Case 33)
109 — Fommel	Male, aged 47, workman Pneumonia at 14 In 1903 severe pain and commencing gangrene in right foot with absence of pulsation in right anterior tibial artery Pirigoff's operation performed In 1906 polycythemia and cyanosis	Cyanosed Spleen not enlarged Heart normal Blood-pressure normal Veins dilated Arteries rigid Fingers clubbed Patient thin	Red cells 9,700,000 Hemoglobin 150 Later red cells 10,200,000, white cells 5,300 Poly neutrophils 71.8 per cent, lymph 19.3 per cent, trans 3.7 per cent, eosin 0.6 per cent Color index 0.78	No other data

Very general cyanosis Spleen and liver not palpably enlarged Heart's impulse powerful, first and second sounds heard over whole cardiac area, systolic murmur constant at pulmonic area, inconstant at apex Great clubbing of fingers and toes Temperature usually subnormal Slight edema of legs at times Urine contained a trace of albumin on one occasion

11. 12. 13. 14. 15. 16. 17. 18. 19. 20. 21. 22. 23. 24. 25. 26. 27. 28. 29. 30. 31. 32. 33. 34. 35. 36. 37. 38. 39. 40. 41. 42. 43. 44. 45. 46. 47. 48. 49. 50. 51. 52. 53. 54. 55. 56. 57. 58. 59. 60. 61. 62. 63. 64. 65. 66. 67. 68. 69. 70. 71. 72. 73. 74. 75. 76. 77. 78. 79. 80. 81. 82. 83. 84. 85. 86. 87. 88. 89. 90. 91. 92. 93. 94. 95. 96. 97. 98. 99. 100. 101. 102. 103. 104. 105. 106. 107. 108. 109. 110. 111. 112. 113. 114. 115. 116. 117. 118. 119. 120. 121. 122. 123. 124. 125. 126. 127. 128. 129. 130. 131. 132. 133. 134. 135. 136. 137. 138. 139. 140. 141. 142. 143. 144. 145. 146. 147. 148. 149. 150. 151. 152. 153. 154. 155. 156. 157. 158. 159. 160. 161. 162. 163. 164. 165. 166. 167. 168. 169. 170. 171. 172. 173. 174. 175. 176. 177. 178. 179. 180. 181. 182. 183. 184. 185. 186. 187. 188. 189. 190. 191. 192. 193. 194. 195. 196. 197. 198. 199. 200. 201. 202. 203. 204. 205. 206. 207. 208. 209. 210. 211. 212. 213. 214. 215. 216. 217. 218. 219. 220. 221. 222. 223. 224. 225. 226. 227. 228. 229. 230. 231. 232. 233. 234. 235. 236. 237. 238. 239. 240. 241. 242. 243. 244. 245. 246. 247. 248. 249. 250. 251. 252. 253. 254. 255. 256. 257. 258. 259. 260. 261. 262. 263. 264. 265. 266. 267. 268. 269. 270. 271. 272. 273. 274. 275. 276. 277. 278. 279. 280. 281. 282. 283. 284. 285. 286. 287. 288. 289. 290. 291. 292. 293. 294. 295. 296. 297. 298. 299. 300. 301. 302. 303. 304. 305. 306. 307. 308. 309. 310. 311. 312. 313. 314. 315. 316. 317. 318. 319. 320. 321. 322. 323. 324. 325. 326. 327. 328. 329. 330. 331. 332. 333. 334. 335. 336. 337. 338. 339. 340. 341. 342. 343. 344. 345. 346. 347. 348. 349. 350. 351. 352. 353. 354. 355. 356. 357. 358. 359. 360. 361. 362. 363. 364. 365. 366. 367. 368. 369. 370. 371. 372. 373. 374. 375. 376. 377. 378. 379. 380. 381. 382. 383. 384. 385. 386. 387. 388. 389. 390. 391. 392. 393. 394. 395. 396. 397. 398. 399. 400. 401. 402. 403. 404. 405. 406. 407. 408. 409. 410. 411. 412. 413. 414. 415. 416. 417. 418. 419. 420. 421. 422. 423. 424. 425. 426. 427. 428. 429. 430. 431. 432. 433. 434. 435. 436. 437. 438. 439. 440. 441. 442. 443. 444. 445. 446. 447. 448. 449. 450. 451. 452. 453. 454. 455. 456. 457. 458. 459. 460. 461. 462. 463. 464. 465. 466. 467. 468. 469. 470. 471. 472. 473. 474. 475. 476. 477. 478. 479. 480. 481. 482. 483. 484. 485. 486. 487. 488. 489. 490. 491. 492. 493. 494. 495. 496. 497. 498. 499. 500. 501. 502. 503. 504. 505. 506. 507. 508. 509. 510. 511. 512. 513. 514. 515. 516. 517. 518. 519. 520. 521. 522. 523. 524. 525. 526. 527. 528. 529. 530. 531. 532. 533. 534. 535. 536. 537. 538. 539. 540. 541. 542. 543. 544. 545. 546. 547. 548. 549. 550. 551. 552. 553. 554. 555. 556. 557. 558. 559. 560. 561. 562. 563. 564. 565. 566. 567. 568. 569. 570. 571. 572. 573. 574. 575. 576. 577. 578. 579. 580. 581. 582. 583. 584. 585. 586. 587. 588. 589. 590. 591. 592. 593. 594. 595. 596. 597. 598. 599. 600. 601. 602. 603. 604. 605. 606. 607. 608. 609. 610. 611. 612. 613. 614. 615. 616. 617. 618. 619. 620. 621. 622. 623. 624. 625. 626. 627. 628. 629. 630. 631. 632. 633. 634. 635. 636. 637. 638. 639. 640. 641. 642. 643. 644. 645. 646. 647. 648. 649. 650. 651. 652. 653. 654. 655. 656. 657. 658. 659. 660. 661. 662. 663. 664. 665. 666. 667. 668. 669. 670. 671. 672. 673. 674. 675. 676. 677. 678. 679. 680. 681. 682. 683. 684. 685. 686. 687. 688. 689. 690. 691. 692. 693. 694. 695. 696. 697. 698. 699. 700. 701. 702. 703. 704. 705. 706. 707. 708. 709. 710. 711. 712. 713. 714. 715. 716. 717. 718. 719. 720. 721. 722. 723. 724. 725. 726. 727. 728. 729. 730. 731. 732. 733. 734. 735. 736. 737. 738. 739. 740. 741. 742. 743. 744. 745. 746. 747. 748. 749. 750. 751. 752. 753. 754. 755. 756. 757. 758. 759. 760. 761. 762. 763. 764. 765. 766. 767. 768. 769. 770. 771. 772. 773. 774. 775. 776. 777. 778. 779. 780. 781. 782. 783. 784. 785. 786. 787. 788. 789. 790. 791. 792. 793. 794. 795. 796. 797. 798. 799. 800. 801. 802. 803. 804. 805. 806. 807. 808. 809. 810. 811. 812. 813. 814. 815. 816. 817. 818. 819. 820. 821. 822. 823. 824. 825. 826. 827. 828. 829. 830. 831. 832. 833. 834. 835. 836. 837. 838. 839. 840. 841. 842. 843. 844. 845. 846.

Male, aged 52, miner. Father died of bronchitis, mother of heart disease. One sister of phthisis in early adult life. Patient very moderate in use of alcohol and tobacco. Attack of right sided pleurisy at 35 and another at 16. No hectic or malairial history. Present illness began in Nov., 1903, with swelling and pain in abdomen, vomiting, eructations, weightlessness and loss of eight fluid complexion for three

Watson-  
Wemyss

*Male, aged 55 Admitted to Royal Infirmary under Dr Gibson Feb 27, 1909, complaining of giddiness, pain in head (especially right side), pain vomiting Family history unimportant, no venereal history urine always healthy except typhoid fever in youth Four months ago attacks of giddiness lasting thirty seconds and accompanied by severe pain right frontal region and dimness of vision in right eye Also vomiting without reference to food*

Complexion florid but hardly cyanosed, lips and tongue highly colored. Neither spleen nor liver enlarged. Lungs normal. Heart slightly enlarged, blood vessels thickened and tortuous. Blood-pressure 130. Conjunctivæ injected and superficial venules much engorged and dilated, fundus much darker than normal, and vessels greatly engorged with very dark blood. No trace of optic neuritis. Urine shows trace of albumin.

Very general cyanosis Spleen and liver not palpably enlarged Heart's impulse powerful, first and second sounds heard over whole cardiac area, systolic murmur constant at pulmonic area, inconstant at apex Great clubbing of fingers and toes Temperature usually subnormal Slight edema of legs at times Urine contained a trace of albumin on one occasion

ected to umbilicus      Splenic  
heart slightly enlarged      Liver and  
moderately thickened      Vessels  
sure 130      Blood-pres-

In November, 1905, red cells 4,590,000 Hemoglobin 87 White cells 10,300 Polys 69.5 per cent, lymph 22.5 per cent, large mono 4 per cent, eosin 4 per cent Color index 0.94 In 1908 red cells 8,870,000 to 10,- 870,000 Hemoglobin 106 to 110 Later red cells went as high as 13,250,000 Hemoglobin 120 Color index 0.47

Red cells on nine counts varied from 7,950,000 to 9,100,000 Hemoglobin 110 White cells 9,200 to 15,500 Polys 75-88 per cent Lymph 7-17 per cent Large mono 2-6 per cent Eosin 2-6 per cent Mast cells 1-4 per cent Giant increase in viscosity

blood in spleen Permanent effect  
excellent health Patient now in  
Thirst, vomiting and constipation  
greatly alleviated by diet and drug  
treatment No other treatment of  
value K I useless and arsenic  
aggravated symptoms Lactogen  
helped milk (1½ pints daily) only  
dation of intestinal tract Patient  
left hospital with subjective symp-  
toms entirely arrested and at pres-  
ent is in excellent health, but poly-  
cythemia still persists

*Patient improved under treatment in hospital with rest, warmth, venesection, saline infusions, iodids and arsenic*

TABLE 3 — (Continued)

| Case No<br>and Author* | History   | Examination   | Blood Examination  | Outcome, Treatment, Autopsy and<br>Remarks  |
|------------------------|---|---|--|---|
| 113 —<br>Milch-<br>ner | Male Case of polycythemia with splenomegaly shown by Dr Milchner before the Berlin Medical Society. The patient sought advice on account of dyspnea and pain in left hypochondrium                                    | Remarkably red face<br>Spleen enlarged<br>Urine contained eight times the normal amount of iron   | Polycythemia present<br>number of red cells stated   | Venesection proved useless, red cells increasing again after a few hours<br>X-ray to spleen unsuccessful<br>Diet containing as little ferruginous material as possible benefited patient's general condition. Milchner states that, of 7,000 patients examined in out-patient department Royal Medical Clinic three were cases of erythremia  |
| 114 —<br>Manges        | Female, aged 26 Symptoms began acutely three or four months ago with vomiting Three weeks later swelling of left side and ascites, and because of this and increased weakness she entered hospital Was never cyanosed | No cyanosis<br>Spleen reached to umbilicus, was hard and with a number of large nodules on its surface<br>Liver enlarged, hard and with a regular border Considerable ascites and slight jaundice<br>Heart Slight systolic murmur and moderate enlargement of both ventricles<br>Low grade fever constantly present<br>Was sermann negative | Red cells 6,500,000 to 8,000,000<br>Hemoglobin 120<br>White cells 35,000   | Clinical diagnosis favored Hanot's hyperritrophic cirrhosis but such a diagnosis untenable on account of blood picture Final diagnosis was an unusual form of polycythemia in which jaundice, ascites, fever, absence of cyanosis and an unusually rapid course were the unusual features Possible association of hyperritrophic cirrhosis and thrombosis of splenic veins occurring during course of polycythemia also referred to |
| 115 —<br>Horder        | Male, aged 51 Healthy until five years ago when enlargement of spleen began to cause discomfort A year later signs of polycythemia became pronounced  | Spleen enlarged   | Red cells 10,700,000<br>Hemoglobin 130<br>Color index 0.61<br>Later, nine days after venesection for fifth time, red cells 9,500,000 | Horder regards disease as morbid entity involving composition and distribution of blood Venesection, large amounts being withdrawn, gave constant although transient relief, red cells falling three or four million and other disturbances becoming attenuated after each blood letting It was repeated six times in two months, from 150 to 700 c c of blood being withdrawn  |



TABLE 3 — (Continued)

| Case No<br>and Author * | History  | Examination  | Blood Examination  | Outcome, Treatment, Autopsy and<br>Remarks   |
|-------------------------|--|--|--|--|
| 120 —<br>White          | Female, aged 57, single Had in the past suffered from neuritis and erythema and had lost 28 pounds in weight in a comparatively short time Suffered from severe irregular abdominal pain and some flushing of hands A large tumor proved on exploration to be an enlarged spleen | No cyanosis, patient a trifle drawn and pale Spleen reached $4\frac{1}{2}$ inches below costal margin and an accessory spleen was present Some dilatation of blood-vessels                         | A few days after the operation red cells were 7,375,000, hemoglobin 90 per cent, color index 0.62 and white cells 43,400 Three and one half months after operation red cells 9,546,000, hemoglobin 117 and white cells 46,350 Color index 0.61 | Operation on August 27, 1911, disclosed a moderately enlarged spleen Close to the anterior margin was an accessory spleen somewhat larger than a fifty shilling piece For seventy-two hours after the operation there was an exceptional oozing of blood |
| 121 —<br>White          | Female, aged 28 Healthy until three years ago when began to have pain and discomfort in left hypochondrium sufficient to prevent her doing housework Eighteen months ago abdomen opened and tumor found to be enlarged spleen  | Nothing abnormal in appearance, and examination revealed only that spleen reached to 2 inches below umbilicus and forward to within an inch of the umbilicus Blood-pressure 134 Optic disks normal | Red cells 8,600,000 Hemoglobin 100 White cells 7,000 Polys 62 per cent Lymph 24 per cent Spleen 12 per cent Eosin 2 per cent Color index 0.58  |  |
| 122 —<br>Kuttner        |  | Face red Spleen finger's breadth below costal margin Blood pressure 140  | Red cells 5,000,000 to 6,000,000 Hemoglobin 85 White cells 13,500 Polys 64 per cent Lymph 35 per cent Eosin 1 per cent   |  |
| 123 —<br>Stachelin      | Male, aged 35 For one and a half years congestion of the head, and sense of oppression of heart after exercise   | Reddish color Spleen showed pericystic enlargement Liver not enlarged Heart not enlarged Blood-pressure 140  | Red cells 6,170,000 Hemoglobin 162 Color index 1.57  |  |

Male, aged 52, Russian Jew, grocer  
 age of 20 In childhood Pleurisy at  
 with uneventful recovery Later  
 headache, vertigo, hazy vision and  
 fulness in head General health  
 fairly good until May, 1910, when  
 began to have attacks of right sided  
 headache with dizziness and short  
 ness of breath Following these at-  
 tacks hands, face, lips and nose be-  
 came dusky, duskiness lasting two  
 to twenty four hours In Autumn,  
 1910, frequent attacks of indiges-  
 tion preceding attacks of cyanosis  
 and headache Since January, 1911,  
 marked impairment of vision, dizziness  
 and hump in throat on swallowing  
 has been of reddish color since his  
 youth but only cyanosed for two  
 years

Male, aged 43, Russian Jew, vest  
 maker For four years in the army,  
 then for twenty years a vest maker  
 in the United States Asthma and  
 cough for 15 years Headache for  
 six years Hemorrhoids fifteen  
 months ago operation for same ten  
 months ago Somewhat near sighted  
 three months ago slight hemoptysis  
 two weeks ago slight hemoptysis  
 headache, dizziness and nervousness  
 two days ago his wife noticed that  
 his color had changed

\*For references see text

Face and especially nose, lips, cheeks  
 and ears bluish-red, hands, wrists  
 and arms to elbow bluish red, phar-  
 ynix purplish red, tongue and soles  
 of feet red Spleen not palpable al-  
 though it has been just barely so at  
 times during an exacerbation Lungs  
 slightly emphysematous Heart nor-  
 mal Blood pressure 120 Fingers  
 clubbed with slightly curved nails  
 X-ray shows many enlarged medias-  
 tinal glands Eyes at first showed  
 double optic neuritis, later showed  
 disk Urine shows trace of albumin  
 and a few urates, epithelial cells  
 and leukocytes Hemorrhoids pres-  
 ent

Face and especially lips and ears  
 somewhat dusky Whole face  
 markedly so when lies down face  
 slightly cyanosed Tongue very red  
 and buccal mucosa and pharynx  
 bluish-red Temperature 99.4 on  
 admission and 98.4 the following  
 day Pulse 118 on admission and  
 96 following day Respiration 32  
 Blood-pressure 132 Spleen not  
 enlarged Liver not enlarged Lungs  
 and heart apparently normal  
 Eyes See "Remarks"

Red cells 5,200,000 to 8,660,-  
 000 Hemoglobin 96-140  
 White cells 6,800 to 10,200  
 Polys 54-74 per cent  
 Lymph 15-27 per cent  
 Hyaline 7-15 per cent  
 Eosin 2-9 per cent Myelo-  
 cytes on one occasion 6 per  
 cent No nucleated reds  
 Viscosity markedly in-  
 creased Blood very dark

Cyanosis has changed very little since  
 he was first observed by Lucas in  
 May, 1911 On a number of  
 occasions venesection has been  
 performed, sixteen ounces of blood  
 being withdrawn as a rule, with  
 some temporary improvement in blood  
 general condition but without any  
 marked effect on cyanosis and with-  
 out any permanent improvement in  
 the blood count Patient states that  
 he has bleeding from the bowel at  
 intervals of six weeks or more with  
 temporary relief

Red cells 8,430,000 Hemoglo-  
 bin over 120 White cells  
 8,800

See text for treatment Six months  
 after patient was first seen his con-  
 dition was unchanged He had sev-  
 eral exacerbations during this time  
 Twice the symptoms were sufficient-  
 ly severe to require venesection,  
 which gave prompt but temporary  
 relief Eye examination revealed  
 only a marked congestion of the  
 conjunctiva and retina



| TABLE 4 (CLASS D) —CASES WITH EITHER CYANOSIS OR SPLENOMEGALY ABSENT AND WITH A SPECIAL HISTORY |   |  |  |   |  |
|---|---|--|--|---|--|
| Case No and Author*   | History   | Examination  |  | Blood Examination   | Outcome, Treatment, Autopsy and Remarks  |
|   |   | Slight enlargement of the heart little irregularity of cardiac action Blood pressure 170 Atherosclerotic gangrene of foot Blood pressure 150 to 160 Urine shows a trace of albumin Cyanosed Heart enlarged pressure 210 Urine shows a trace of albumin Atherosclerosis Hemorrhagic glaucoma Blood pressure 190 Heart enlarged Contracted kidney Blood pressure 250 |  | Red cells 6,100,000 Hemoglobin 108 Color index 0.89   |  |
| 126 — Geisbock  | Male, aged 55, bank director Patient overworked and very excitable Run of blood to head at times                                    | Blood pressure 170 Atherosclerotic gangrene of foot  |  | Red cells 10,400,000 to 11,320,000 Hemoglobin 156   | Improved after use of iodothyron, the blood pressure falling to 120                                    |
| 127 — Geisbock  | Male, aged 64 Hard work and some indulgence in alcoholic liquor Gangrene of right foot with amputation                              | Blood pressure 150 to 160 Urine shows a trace of albumin   |  | Red cells 7,100,000 to 8,000,000 Hemoglobin 112   | Dorsalis pedis artery of the amputated foot was extremely sclerotic                                    |
| 128 — Geisbock  | Male, aged 62, conductor Right sided hemiplegia   | Cyanosed Heart enlarged pressure 210 Urine shows a trace of albumin  |  | Red cells 6,930,000   |  |
| 129 — Geisbock  | Male, aged 60 Patient excitable   | Atherosclerosis Hemorrhagic glaucoma Blood pressure 190  |  | Red cells 6,840,000 Hemoglobin 120 Color index 0.89   |  |
| 130 — Geisbock  | Male, aged 53, factory manager Patient overworked and subject to apoplectic seizures with disturbance of speech                     | Heart enlarged Contracted kidney Blood pressure 250  |  | Red cells 8,170,000 Hemoglobin 128 Color index 0.78   |  |
| 131 — Geisbock  | Male, aged 49, architect Overworked and subject to apoplectic attacks   | Heart enlarged Blood-pressure 170 to 220   |  | Red cells 6,030,000, hemoglobin 104 Color index 0.86  |  |
| 132 — Geisbock  | Male, aged 59, civil officer History of lues and sexual excess Right hemiplegia   | Blood pressure 180   |  | Red cells 6,000,000   |  |
| 133 — Geisbock  | Male, aged 56, commissioner History of asthma   | Heart enlarged Blood-pressure 170 Polyuria and albuminuria   |  | Red cells 6,165,000 Hemoglobin 120 Color index 0.97   |  |
| 134 — Geisbock  | Male, aged 56, factory manager  | Heart enlarged Contracted kidney Blood-pressure 235 Urine shows albumin  |  | Red cells 7,030,000   |  |
| 135 — Geisbock  | Male, aged 45   | Heart enlarged Blood-pressure 180 Trace of albumin in urine  |  | Red cells 6,000,000   |  |
| 136 — Geisbock  | Female, aged 52   | Heart enlarged Blood-pressure 200  |  | Red cells 6,575,000 Hemoglobin 125 Color index 0.95   |  |
| 137 — Geisbock  | Female, aged 45   | Heart enlarged Blood-pressure 220 Trace of albumin in urine  |  | Red cells 6,000,000 Hemoglobin 112 Color index 0.93   |  |
| 138 — Geisbock  | Male, aged 46   | Heart enlarged Blood-pressure 250 Atherosclerosis Contracted kidney, albumin and casts in urine  |  | Red cells 5,700,000 Hemoglobin 104 Color index 0.91   |  |
| 139 — Geisbock  | Male, aged 51   | Red face Heart slightly enlarged Blood pressure 195 Albuminuria  |  | Red cells 5,700,000   |  |
| 140 — Geisbock  | Male, aged 51 Admitted with cerebral hemorrhage   | General cyanosis Slight emphysema Heart slightly hypertrophied Distention superficial veins Blood pressure 190 A little albumin and a few hyaline casts  |  | Red cells 7,500,000 Hemoglobin 180 White cells 19,000 Differential normal No nucleated red cells Color index 1.20 |  |
| 141 — Heck  | Female, aged — Complains of head ache, giddiness, palpitation, buzzing in ears and occasional slight bleeding from mucous membranes | Marked cyanosis Heart enlarged, especially to left, vessels slightly sclerosed Blood pressure 310 No   |  | Red cells 7,750,000 Hemoglobin 140 White cells 4,000 Color index 0.9  | These two cases (142 and 143) mentioned in medical journal only as short society abstracts without any |
| 142 — Mohr  | Female, aged 42 Complained of dyspnea and palpitation   | Marked cyanosis Heart enlarged, especially to left, vessels slightly sclerosed Blood pressure 310 No   |  | Red cells 7,750,000 Hemoglobin 140 White cells 4,000 Color index 0.9  |  |

Rover's article presents the findings in two new cases of polycythemia studied with the hemodynamic method, the findings being tabulated under twenty-two headings and showing how the circulatory conditions differ in different patients and in the same patient at different times. Rover's article also teaches that high saturation of the venous blood with oxygen is of evil import in polycythemia as well as in other disease

ment blood letting and inhalations of oxygen

Splenic enlargement materially increased from September last, when it was at the anterior border of spleen, to the umbilicus, to present right mammary line. Brill calls attention to the absence of cyanosis, notwithstanding the erythrocytosis, as well as to the accompanying leucocytosis which he thinks may suggest a leukemia of the myeloblastic type. He also calls attention to the low percentage of hemoglobin

Rover's article presents the findings in two new cases of polycythemia studied with the hemodynamic method, the findings being tabulated under twenty-two headings and showing how the circulatory conditions differ in different patients and in the same patient at different times. Rover's article also teaches that high saturation of the venous blood with oxygen is of evil import in polycythemia as well as in other disease

Outcome, Treatment, Autopsy and Remarks

Blood Examination

Examination

History

Case No. and Author\*

150 — Great polycythemia following long continued use of Levico water, which contains iron and arsenic

Dronke and Ewald

Male, aged 57 Supposed to have acute Addison's disease with great anemia Gradual improvement, oligocythemia giving way gradually to polycythemia and later the number of red cells falling to normal

151 — Neumann

Red cells in December, 1891, slightly over 5,000,000 In January, 1892, red cells 8,400,000 and hemoglobin 85

Red cells in April, 1895, 1,120,000 Gradually increased, reaching 7,700,000 in following January and falling to 5,000,000 in July

Red cells 6,000,000 to 7,600,000 A few months later fell to 4,000,000 while a year previous had been 3,400,000 Resistance to hemolysis above average

Red cells upper part of body 5,400,000 to 6,700,000, lower part of body from 4,400,000 to 6,000,000 White cells 6,900 to 15,000 upper part of body and 8,100 to 12,000 lower part

Transitory cyanosis Spleen enlarged

Female, aged 10 Chronic jaundice of variable degree with urobilinuria and splenomegaly Transitory cyanosis and polycythemia accompanied exacerbation of jaundice

Cyanosis limited to territory of superior vena cava until well towards end of life Spleen enlarged Veins enlarged Edema eyelids Dyspnea Cervical glands enlarged Liver not enlarged

Male, aged 24 Progressive compression superior vena cava by malignant tumor of the thymus March, 1904, face and neck began to swell, pain in abdomen and chest, cough and expectoration

153 — Reck/eh

Red cells, on three counts in January, 1905, from 10,000,000 to 10,800,000 White cells 10,000 Polymorphonuclear neutrophils 73 per cent

"Patient is a strong man" Moderately cyanosed Spleen not mentioned Complains of swelling of liver Peripheral vessels sclerosed Urine shows some albumin and a few hyaline casts

Male, aged 58 For four years heard ache, dyspnea, palpitation and poor sleep Symptoms gradually became worse and in December last complained of pain and swelling of liver and of diarrhea Is still in the same condition Does not drink De mes venereal infection

This case referred to by Bence as having been treated by oxygen inhalations No particulars

155 — Kornm

Blood Examination

Last count carefully verified by a second count Note low hemoglobin percentage

Weber, referring to this case, says "It is probable that in all cases of anemia from hemorrhage, and other forms of anemia improving without special treatment, the anemia may occasionally give way to temporary polycythemia, as if normal level had been overshoot by reaction of the blood making organs"

Weber thinks this case may be compared in some respects to Hayem's chronic splenomegalic acholuric jaundice with oligocythemia Compares also with Mosse's case (Number 159)

Died with increased dyspnea, edema, venous dilatation, weakness and mental stupor Autopsy Tumor of thymus had extensively involved right lung (possible cause of polycythemia), with metastatic growths in brain, kidneys, pancreas and elsewhere Spleen soft and dark red Bone marrow apparently not examined

This case appears to be identical with Kraus' case (Number 26) and is therefore included in doubtful class to avoid duplication

177 ---  
 Albumin  
 Female, aged 20  
 Splenomegaly from  
 early childhood  
 Cyanosis from age  
 various hemorrhages at 15  
 At 17  
 had enlargement of spleen from  
 childhood  
 Repeated attacks of paroxysmal  
 hemoglobinuria  
 Male, aged 58  
 Patient suffered from  
 chronic splenomegaly, urobilinuria  
 and chronic acholuric jaundice

Autopsy Spleen enlarged and con-  
 tained cyst with sero sanguinous  
 partial Splenic substance showed  
 (leukoblastic, not erythroblastic)  
 Very many cells containing phago-  
 pleural hemorrhage, viscera ex-  
 tremely engorged Bone marrow  
 long bones mostly red and micro-  
 scopically showed proliferation of  
 cellular elements (notably normo-  
 blasts and giant cells but not mast  
 cells)

Polycythemia present

Red cells 6,000,000 to 9,000,000  
 Hemoglobin 110 140

Red cells 6,750,000 to 7,825,000  
 Hemoglobin 100 110

Pel suggests that both the polycythemia and the paroxysmal hemoglobinuria may have been of toxic origin

160 ---  
 Anders

Female, aged 21  
 Neuropathic heredity  
 Menstruation at age of 12  
 Appendectomy at 17  
 At 19 struck by hard fall over right ovary, followed by three abscesses which ruptured into the uterus and was followed by later acute nephritis  
 Menses irregular and somewhat painful  
 Present trouble dates to operation for appendicitis although no cyanosis until curettement  
 Patient weak and neurasthenic

Skin markedly livid, especially face  
 Spleen enlarged  
 Obvious inspiratory dyspnea  
 Heart slightly dilated and an occasional systolic murmur at tricuspid orifice  
 Pulse rapid, small and compressible  
 No edema  
 Urine shows slight trace of albumin  
 Height 5 feet 3 inches  
 Weight 86 pounds

Red cells 4,290,000 to 4,800,000  
 Hemoglobin 120  
 White cells 11,100  
 Blood flows freely  
 Many poikilocytes  
 A few macrocytes and some nucleated red cells  
 All cells overstrain very markedly

Mosse suggests case compares in some respects with cases of polycythemia with splenomegaly and in other respects with Hayem's chronic urobilinuria (without bilirubinuria) and with oligocythemia  
 Mosse's case may also be compared with Guinon, Rist and Simon's case (Number 152)  
 Note that in this case there was practically no increase of red cells although hemoglobin percentage was high

\*For references see text

TABLE 5 — (Continued)

| Case No<br>and Author * | History  | Examination  | Blood Examination  | Outcome, Treatment, Autopsy and<br>Remarks   |
|-------------------------|--|--|--|--|
| 161 —<br>Schneider      | Male, aged 51 Formerly had malaria<br>In April, 1901, found to have polycythemia and splenomegaly Spleen removed in May, 1901 Signs of pneumonia in Dec 1901, followed by progressive pulmonary tuberculosis Died in October, 1902 Not clear that this is a case of erythremia   | Spleen enlarged<br>Patient corpulent   | In April, 1901, red cells 6,000,000, white cells 22,000<br>In June, 1901, red cells 4,500,000, white cells 16,000<br>In April, 1902, red cells again above normal<br>In October, 1902, red cells 1,385,000, white cells 55,400<br>Myelocytes 14 per cent and twice as many nucleated red cells as white cells<br>Red cells 9,500,000 Hemoglobin 180 White cells 27,000 | The removed spleen contained anemic infarcts, capsule thickened from old perisplenitis, but no careful examination made Autopsy Advanced pulmonary tuberculous Dilatation and hypertrophy both sides of heart Myocardial fibrotic changes in left ventricle Aortic atheroma Nephritis Ulcer pyloric region of stomach Marrow of long bones red |
| 162 —<br>Turk           | Patient exhibited by Turk showing high grade of polycythemia, cyanosis and splenomegaly  | Cyanosis of high grade Spleen greatly enlarged   | Red cells 8,400,000 to 9,935,000 Hemoglobin 170 White cells 6,500 to 22,000 Viscosity greatly increased  | This appears to be a case exhibited before a society and, as it was probably later included by Turk in list of cases published in 1903, it is included in this class to avoid duplication  |
| 163 —<br>Hill           | Female, aged 40 Patient very neurotic  | Marked cyanosis of face and extremities Spleen greatly enlarged  | Red cells 11,450,000 Hemoglobin 110 White cells 16,300 Myelocytes 36 per cent No nucleated red cells   | Hill says that the notes on this case were given him by Turk, but without any history It seems probable that it is a duplication of one of Turk's cases and it is therefore included in this class to avoid repetition   |
| 164 —<br>Blumenthal     | Female, aged 31 From two years of age subject to attacks of paroxysmal dyspnea, accompanied by severe headache and followed by copious expectoration From age of 21 cyanosis, debility and hemiplegias   | Cyanosed Heart somewhat hypertrophied, tachycardia Retinal veins tortuous and engorged with blood Exophthalmos | Red cells before operation 7,750,000 Two months later had fallen to normal   | Blumenthal regarded this case as congenital Autopsy Bronchopneumonia, bone marrow red and succulent, leukoblastic tissue marked in excess of erythroblastic  |
| 165 —<br>Holmes         | Male, aged 21 Father died at age of 57 from some abdominal disease While in school patient became weak, dizzy and nervous and after a few months had to go home He was troubled with diarrhea and constipation and was treated for mucous colitis Improved somewhat but attacks of abdominal distress continued One of the attacks was accompanied by so much tenderness over the appendix that the family physician recommended its removal, which was done | No cyanosis remembered Spleen not noticeably enlarged No clubbing of fingers remembered                        |  | Many blood counts showed a high grade of polycythemia without apparent abnormality in the white blood count Polycythemia disappeared entirely shortly after removal of appendix and six months later the patient seemed improved in general  |

166 —

1 cell

Female, aged 37 Long resided in India and had suffered from sun stroke and many attacks of fever In 1901 returned to England and attacks accompanied by shivering at left side and radiating down leg In 1906 had intermittent pyuria with taking sulphonal for years, although none had been prescribed during the nine months prior to her death Male, aged 53 Obesity with extreme tendency to drowsiness

167 —

Munzer

No cyanosis reported No enlargement of spleen detected clinically Urine reported to contain urobilin but later color found to be due to hematuria

Red cells 6,500,000 No leukocytosis

Eventually the patient died with increase of myasthenia and paralysis No autopsy Fells considered this case one of auto-intoxication from the alimentary tract

168 —

Howard

Female, aged 17, married, native of the United States Both parents died of apoplexy Patient always robust and high colored always every three weeks and lasted seven or eight days For five years seven men on exertion and occasional attacks of palpitation and occasional pneumonia during past three attacks since last attack 1 year ago dyspnea constant and at times severe Past 4 or 5 months swelling of legs and pain around the heart During last month several attacks of numbness and stiffness of right arm, left side neck and left arm

Cyanosis present Spleen and liver normal Distention of the neck (see "Remarks")

Red cells 9,800,000 cells 5,500

White

Munzer regarded this as a case of erythrocytosis, probably from blood stasis not of cardiac origin There was distention of the neck which Munzer supposed to be connected with substernal fat or goiter Under thyroid treatment the patient's weight fell from 103 to 89 3 kg and all alarming symptoms disappeared During several months' treatment dilatation of the heart and arterial hypertension partially controlled with amelioration of symptoms Patient's death followed a paroxysm of dyspnea and autopsy could not be secured Towards the end the skin became of a yellowish color

Only cyanosis observed was occasional appearance of bluish tint to lips, face was flushed Spleen never perceptibly enlarged Lungs slightly emphysematous Heart dulness increased but sounds clear and strong Radial arteries stiff Blood-pressure 190 Urine shows trace of albumin

Red cells 5,124,000 to 8,670,000 Hemoglobin 70 130 White cells 8,000 to 40,000 Polys 70-86 per cent, Lymph 12-18 per cent, Eosin 0 6-1 00 per cent Mast cells 0 6-1 00 per cent Stimulation forms present at times and erythroblasts twice Anisocytosis, poikilocytosis and polychromatophilin noted at times Color index 0 46-1 07

\*For references see text

TABLE 5 — (Continued)

| Case No<br>and Author*  | History   | Examination   | Blood Examination  | Outcome, Treatment, Autopsy and<br>Remarks  |
|-------------------------|---|---|--|---|
| 169 —<br>Weber          | Male, aged 22 Cyanosis existed at birth, there seemed to be a patency of the interventricular septum During the early years of his life often had attacks accompanied by exacerbation of the cyanosis which seemed sometimes to be induced by a slight knock or annoyance Could not walk until 4 years old Subject to enuresis Father and mother healthy Twin brother well and strong | Great cyanosis lips, nose, tongue, ears, hands and feet, tongue and lips bluish black Liver, spleen and lungs normal Heart slight systolic murmur Blood pressure 100 Gums bleed easily owing to decayed teeth Urine shows well marked cyclic albuminuria Great clubbing of fingers and toes Impaired capillary circulation in hands shown by long persistence of white marks left by pressure X-ray shows heart enlarged transversely and some widening of aortic shadow to the left Cyanosis present Spleen enlarged | Red cells 10,300,000 Hemoglobin 160 White cells 7,000 Polys 72.2 per cent, Lympho 17.2 per cent, Lympho 22.0 per cent, Intermed 5.4 per cent, Eosin 2.0 per cent, Masts 1.0 per cent Red cells appeared normal Blood very dark colored |   |
| 170 —<br>Loewy          | Middle aged merchant Loewy does not give detailed account and says that this case will be reported elsewhere by Strator   |   | Polycythemia present, no detritus Hemoglobin 204 Blood was taken from median vein and amount of iron in same found to be 115.6 mg  | Remained at hospital three months Treatment by venesection showed a little improvement Not seen again |
| 171 —<br>Comes<br>Gatti | Male, aged 28, workman First complained eight days ago of headache and heaviness in head and of rigidity of the neck and marked vertigo Three days later developed unilateral paresis of left side with some aphasia and transitory diplopia and difficulty in swallowing   | Cyanosis not mentioned Spleen not enlarged Heart left ventricle hypertrophied, galloping rhythm Temporary diplopia Bilateral nystagmus, slight strabismus Muscular spasms on right side Tendon reflexes increased Urine negative  | Red cells, on four counts, 6,200,000 to 7,200,000 Hemoglobin 95-100 White cells 8,400 to 16,500 Polys 76 per cent Lymph 16-22 per cent Mono 4-7 per cent Eosin 1 per cent  |   |
| 172 —<br>Tange          | Male, aged 55 Has had gout About a year ago developed weakness of memory Two weeks before coming to hospital had attack of unconsciousness After that trouble with speech, heavy gait and weakness left hand  | Face red Spleen not enlarged Heart enlarged to the left Urine contains five per cent of sugar, but no albumin   | Red cells 7,020,000 Hemoglobin 100   | Note sugar in urine   |

- 173 —  
Lange  
Male, aged 61 His had several apoplectic attacks during last few years, the last one this Spring, since which time has had left sided body and right angle of mouth, weakness of memory and uncertainty of speech  
Female, aged 60 Palpitation of heart and lumbrigo  
Spleen not enlarged Heart enlarged to left Arteries tense and tortuous Lowered Babinski, increased Patellar reflex Urine shows a few granular casts and a trace of albumin  
Red cells 6,400,000 Hemoglobin 100 No alteration in stained blood picture  
Stachelm
- 174 —  
Stachelm  
Bluish red color Spleen and liver not enlarged Heart trouble present Blood-pressure 176 Urine shows trace of albumin Cyanosis not mentioned able Liver slightly enlarged Spleen palpable Liver slightly enlarged Lungs enlarged to the left Heart slightly enlarged 185 Trace of albumin in urine Cyanosed Neither spleen nor liver enlarged Heart trouble present Blood pressure 140 Cyanosed Neither spleen nor liver enlarged Lungs emphysematous Heart slightly enlarged to the left Much albumin in urine Blood-pressure 215 History lost  
Spleen enormous  
A case of massive tuberculosis of the spleen thought by the authors to resemble clinically cases of splenomegalic polycythemia  
For references see text
- 175 —  
Stachelm  
Male, aged 55 For five years headache, vomiting, pain in gastric region, palpitation of heart and pain in back  
Female, aged 17 Dyspnea, congestion of head, vertigo and headache  
Female, aged 40 Headache and an-gina  
History lost  
Stachelm
- 176 —  
Stachelm  
Red cells 7,300,000 Hemoglobin 155  
Stachelm considers this a case of secondary polycythemia
- 177 —  
Stachelm  
Red cells 8,500,000 Hemoglobin 238  
Stachelm considers this a case of secondary polycythemia resulting from emphysema and nephritis
- 178 —  
Stachelm  
Red cells 7,600,000 Hemoglobin 155  
Stachelm considers this a case of secondary polycythemia resulting from cardiac stasis  
Red cells 8,500,000 Hemoglobin 194  
Stachelm considers this a case of secondary polycythemia as result of emphysema and nephritis  
Red cells about 8,000,000  
No blood count made but general physical features of erythremia  
Stachelm mentions this case and says that the history of the case has been lost  
Regarded by authors as primary tuberculosis of the spleen



TABLE 6 (CLASS F) —THE JOURNALS IN WHICH THE FOLLOWING CASES WERE REPORTED WERE SECURED TOO LATE TO PERMIT OF TRANSLATION OF THE FOREIGN ARTICLES OR FOR THE INCLUSION OF ANY OF THE CASES UNDER THE PROPER CLASSIFICATION

| Case No. and Author* | History   | Examination  | Blood Examination  | Outcome, Treatment, Autopsy and Remarks  |
|----------------------|---|--|--|--|
| 180 — Wasserthal     | Male, aged 28, merchant A case in which dyspeptic symptoms predominated   |  | Red cells 7,400,000 to 7,500,000 Hemoglobin 100 White cells 11,000   |  |
| 181 — Umber          | Male, aged 50   | Blood pressure 138 145 present   | Red cells 11,960,000 Hemoglobin 150 White cells 14,400 Color index 0.63  |  |
| 182 — Umber          | Female, aged 50 Case complicated by diabetes  | Spleen and liver enlarged Blood-pressure 115 Urine shows albumin, casts and 1 per cent of sugar  | Red cells 10,880,000 Hemoglobin 150 White cells 5,700 Color index 0.68   |  |
| 183 — Jones          | Male, aged 56, English For many years severe attacks of migraine and leg, was organically sound and treatment caused disappearance of edema and improvement in migraine Four years ago sudden attack of vertigo and loss of consciousness for about one minute At intervals since has been giddy For several years color intensified Some constipation and slight dyspnea on exertion | Extreme general cyanosis, most marked in ears and lips, which were nearly black Also marked in mucous membranes Gums, tongue, pharynx and inside of mouth all of deep purple color Spleen extended nearly to pubes, not tender, surface smooth and firm Lungs nothing abnormal beyond a few coarse bronchi Heart soft systolic apical murmur without symptoms Conjunctive deeply injected Gums bled easily Blood-pressure 140-160 Urine a faint trace of albumin | Red cells 8,500,000 Hemoglobin 110 White cells 20,000 Color index 0.6 Polys 92 per cent, small lymph 6 per cent, large lymph 12 per cent, eosinophils 0.8 per cent No polkocytes, mast cells or myelocytes | Treated with iodid in form of iodalbumin given daily for a month at a time with a week's intermission He was first seen in March, 1911, and last seen in Oct, 1911, at which time his health was still good, the cyanosis not so marked, the spleen possibly slightly smaller, the cardiac condition satisfactory, the murmur giving rise to no symptoms, and the lungs perfectly normal |
| 184 — Voorsanger     | Female, aged 19, stenographer Entered hospital Oct 9, 1911, complaining of pain in cardiac region for past two years, cyanosis for about one year and weakness for past six months  | Marked cyanosis of skin, lips and mucous membranes Spleen and liver not enlarged Lungs negative Heart somewhat enlarged, tones pure Patellar and plantar reflexes increased Eye grounds negative Urine negative Feces and sputum negative No glandular enlargement   | Red cells 7,920,000 Hemoglobin 120-140 White cells 8,400 Polys 71 per cent, lymph 23 per cent, large mononuc 6 per cent, eosin 0 per cent  | Von Puquet was negative X-ray showed considerable enlargement of heart to the right  |

187 —

Abrahamson

Male, aged 10 Entered hospital complaining of shortness of breath and intense cyanosis of upper half of trunk

Intense cyanosis upper half of trunk  
X-ray examination of the chest showed a mediastinal tumor

Red cells from the ear 10,000,000  
from the toe only 5,000,000

188 —

Hamilton and Morse

Female teacher Childhood Ordinary diseases of childhood, including scarlet fever at 16 followed by "chronic gastritis" In 1908 indigestion and "dyspepsia" In Spring of 1909 attack of "grip" and noticed increase in size of waist and "lumped" appearance of skin In Nov., 1909, severe attack indigestion with extreme constipation Menses ceased in Aug., 1909, since then frequent nose bleed

Skin yellowish and at times markedly cyanotic Spleen reached to point halfway between costal margin and umbilicus Liver reached halfway to umbilicus Lungs and heart apparently normal Spleen slightly enlarged with yellow Herpes zoster on right side, vaginal and rectal examination negative Urine normal except for slight trace of bile

Red cells 7,108,000 to 8,000,000 Hemoglobin 85-95  
White cells 8,400 to 9,400  
Polys 80-82 per cent  
small mononuc 10-14 per cent  
cent, large monos 4 per cent  
eosinophils 1-3 per cent  
Slight poikilocytosis Red cells stain lightly A few microcytes No nucleated cells Platelets not increased

187, 188 and 189 —  
Bergman and Petch  
Tabulated findings given in three cases of polycythemia Examined with same detail as Senator's patient

\*For reference see text

This case was referred to by Dr. Abrahamson in the discussion of Dr. Voorssanger's paper as illustrating the difficulty of differentiating true polycythemia from local polycythemia. Autopsy showed tumor to be a sarcoma pressing on the vena cava, which was undoubtedly the cause of the local polycythemia. Treatment with tonic baths, increasing doses of K I and careful diet caused some decrease in size of liver and some general improvement, as did also x-ray, massage and out door exercise. On March 17, 1910, patient vomited six quarts of blood in four hours and died with signs of acute hemorrhage and collapse. Autopsy showed marked evidence of hyperplasia of red cells in the bone marrow, evidence of blood formation in spleen, liver and retroperitoneal lymph nodes and marked cutaneous hemorrhage apparently due to esophageal hemorrhage. Autopsy inclined to regard the polycythemia as compensatory in some cases.

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# VERRUGA PERUVIANA AND ITS COMPARATIVE STUDY IN MAN AND THE APE

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The fact that the Panama Canal is to be opened shortly calls our attention to a disease that may be of more or less interest and importance to Americans in the next few years. Even before the Spanish occupation of South America a peculiar sickness was endemic over a certain inland portion of Peru. The Spaniards suffered terribly from its ravages, as have the natives since then, and the trouble is still present in this same region. At the time of the building of the Oroya Railroad through this country in 1871, the workmen were afflicted greatly with a severe fever termed Oroya fever, and from *Verruga peruviana*. Clinicians finally began to have the feeling that the two diseases were one and the same, though in a different type, and in 1885 a young medical student, Daniel Carrion, allowed himself to be inoculated with the blood of a patient suffering from the latter affection, and in thirty-nine days he was dead from a typical attack of Oroya fever<sup>1</sup>. The heroic young man apparently settled all doubt as to the entity of the two diseases, though, as I will mention later, the question is once more under discussion.

Through a peculiar happening the Berne Dermatology Clinic had what was probably the only case of this trouble ever seen in Europe in the person of a Swiss mountain guide from Zermatt. In 1909, along with a companion, he assisted Miss Annie E. Peck<sup>2</sup> in climbing Huascaran Mountain in Peru. Through misfortune on their way down they were forced to stop twelve days on the ice fields, and his companion had his hands and feet so badly swollen that the two guides were forced to remain some time in Peru before their return to Switzerland.

About one week after his arrival in Zermatt the patient began to notice fleeting symptoms of an uncomfortable feeling, followed by sweating, when in a hot room. They only lasted five or ten minutes, and he was not aware of any temperature disturbance. A little later he noticed a small growth on his left leg and shortly afterwards quite a few came

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\*From the Dermatology Clinic in Berne, Switzerland (Director, Professor Dr. Jadassohn).

1 For the history, clinical symptoms, etc., of this interesting disease I have drawn largely from the complete and well written monograph of Prof. Ernesto Odriozola, "*La Maladie de Carrion*" ou "*La Verruga Peruvienne*" Paris, Georges Carré, et C., Naud, 1898.

2 Peck, Annie E. Harper's Monthly Magazine, January, 1909.

out on his face, arms and hands, and the patient on advice consulted Prof Jadassohn in the Beine Clinic. He had had no other symptoms, and on admittance to the hospital seemed to be perfectly well, except for the tumors. I will not go into detail of what has been already described,<sup>3</sup> but suffice it to say that thorough physical examination showed absolutely nothing pathological outside of the cutaneous growths. The blood-picture was absolutely normal, the Wassermann reaction negative and the von Piquet cutaneous test for tuberculosis and subcutaneous injections of tuberculin in varying amounts up to 1.0 mg. also showed nothing. Some of the tumors were excised for histological examination and inoculation experiments, others were treated with carbon dioxide snow, pyrogallie ointment, tincture of iodine, etc., and in about three weeks it was impossible to prevail on the patient to remain any longer in the hospital, as he was feeling perfectly well and the lesions had practically healed. And since his departure occasional reports show that, outside of a few rheumatic symptoms, he has been quite well.

#### ETIOLOGY

The mountain climbers on their trip had just touched the edge of the verruga territory, but it was apparently enough to transmit the infection. The disease is limited to an inland portion of Peru, from 28 to 60 kilometers from the seaboard. The country is quite mountainous in character, varying in altitude from 400 to 3,000 meters. Curiously enough, the present limits of the disease are somewhat smaller than at the time of the Spanish occupation. The valleys are deep and hot, while the streams are sluggish and many swamps abound. Odriozola thinks that the climate may have some etiological importance, while the water is blamed by others. However, cases have been known to occur in patients who have used nothing but potable water, and, moreover, in April,<sup>4</sup> when the water recedes, the verruga cases augment. No race, age or sex is spared, and Odriozola says that the horses, mules, dogs, llamas, chickens, etc. have symptoms closely allied to those of the human beings. Cases have been cited where the patients have staid but one-half an hour or an hour in the verruga territory and there is at present a feeling that, as in many other tropical diseases, some insect may have something to do with the transmission of the disease. The affection is inoculable, though not contagious, and it is apparently transmissible by the placenta. The incubation period varies from fifteen to forty days, or even longer. In Carrion's case it was twenty-one days, perhaps due to the fact that he was inoculated intravenously, while in Jadassohn's patient it was at least sixty days. Apparently one attack gives immunity for the rest of life.

<sup>3</sup> Jadassohn J. and Seiffert G. Ein Fall von Verruga peruviana, gelungene Übertragung auf Affen. *Ztschr. f. Hyg. u. Infektionskr.* 1910 lxxvi, 247.  
<sup>4</sup> Brault J. La Verruga du Pérou. *La Pratique Dermatologique*, ix, 832.



## SYMPTOMS

In the severe type of the affection, the so-called Oroya fever, the disease is usually ushered in with a chill accompanied by a fever, after prodromal symptoms of headache, general malaise and pain in the joints and muscles<sup>5</sup>. The fever may go up to 40 C (104 F), or even higher, and is accompanied by nausea, vomiting, rapid anemia, sleeplessness, vertigo, hemorrhages, coma and death. The glands are enlarged and the liver and spleen engorged. If the termination be good, the temperature gradually falls and the symptoms lessen. The fever is either remittent, intermittent or irregular in type and may accompany, precede or follow the appearance of the cutaneous manifestations. The pulse is frequent, soft, compressible and, even with a temperature of normal, it may be 120 to 140, or even higher. Among the types of hemorrhage, enterorrhagia is rare, and usually comes along towards the termination of the disease, being an unfavorable prognostic sign. Epistaxis is a very common symptom and petechiae are frequent. Sweating is profuse, especially in the fever of an intermittent type. Edema of the toes and legs is generally found, though it is rarely generalized except in the grave cases. Nervous symptoms of vertigo, syncope, cephalalgia, delirium, insomnia and hic-cough are sometimes seen.

Pneumonia, enteritis, enterocolitis and hemorrhages are among the complications most frequently encountered, though several cases of verruga meningitis have been reported. Occasionally malaria and verruga are seen in the same patient at the same time.

## ERUPTION

The cutaneous eruption is of two general types "*mihane*"<sup>6</sup> or tuberculous, and "*mulaire*" or nodular. Under the first a tubercular, a sudaminal, a vesicular and a pustular efflorescence are noted. The eruption may be localized, generalized, discrete or confluent, and the favorite seats with the tubercular or "*mihane*" efflorescence are the anterior regions of the legs, extensor surfaces of the forearms, antero-extensor surfaces of the arms, forehead, jaws, nose, eyebrows, knees and elbows. The mucous membranes of the eyes, mouth, digestive and genito-urinary tracts are also frequently involved. Moreover, verruga nodules have been found in the peritoneal coats, spleen, liver, pancreas, kidneys, lungs, muscles, and central nervous system. The "*mulaire*" or nodular lesions are subdermic, varying in size from a walnut to a small orange, and they may be sessile.

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5 Prof Odriozola proposes to divide the disease into two types, according as the fever or as the cutaneous tumors predominate in the symptoms. The first type he would call "Oroya fever" or "*Fiebre de Carrion*," and the latter "*Eruption de Carrion*"—thus naming the disease after the young martyr.

6 The words "*mihane*" meaning tubercular and "*mulaire*" meaning nodular have been taken over bodily from the Spanish by Prof Odriozola.

or pedunculated. They are never internal and are found on the eyelids, cheek-bones, lobules of the ears, bridge of the nose and the knees. Jadassohn's patient had examples of both the "*milium*" and the "*Milium*" efflorescences—confined mostly to the face, arms and legs. The conjunctiva of one eye was affected, but otherwise the mucous membranes showed nothing. The patient also showed a macular eruption resembling a lupus and thus far not described in connection with verruga peruviana.

#### PATHOLOGY AND BACTERIOLOGY

In regard to the pathology and bacteriology of the disease, much still remains to be desired, because of the marked differences in the findings of investigators. The blood-picture is that of a rapid and marked anemia. Bassett-Smith<sup>7</sup> found an abundance of nucleated red cells, and the erythrocytes were irregular in their size, shape and staining qualities. Many basophilic granulations were seen and a few myelocytes were present. The bone-marrow usually shows signs of proliferation. The liver and spleen are generally engorged and the latter organ occasionally extends down to the iliac fossa. It is soft and more or less friable, while the liver is slaty in color, as in malaria due to the destruction of red cells. The lymphatic ganglia are greatly engorged, those of the mesentery occasionally reaching the size found in tuberculous peritonitis and leukocythemia. The urine is merely feeble. Histologically, Nicolle<sup>8</sup> found small nodules of epithelioid cells in the liver and lungs, but no caseation. In the lymph-nodes he found true caseation in their centers, but no giant cells. Somewhat analogous though more marked lesions were noted in the spleen. DeVecchi<sup>9</sup> found early hemorrhagic lesions in the spleen, lungs, liver, muscles and skin along with new tissue formation. In the liver there was a vacuolization of the elements and compression of the cells by the widening of the vessels and by the formation of verruga nodules. Pigment clumps were also noted and phagocytic leukocytes were noted in both the liver and spleen. He found giant cells in both these organs and in the lungs there were appearances of new tissue formation and small areas of bronchopneumonia. The cutaneous lesions have been studied by several men and it seems to be the consensus of opinion that they are granulomatous in type, made up of fibroblasts, mono- and polymorphonuclear leukocytes, plasma and red cells. The tumors are very vascular and later show signs of necrosis. Acid-fast bacilli have been found in the internal lesions by Nicolle,<sup>8</sup> and also by

<sup>7</sup> Bassett-Smith, P. W. The Pathology of the Blood in Verruga. Brit Med Jour., Sept. 18, 1909.

<sup>8</sup> Nicolle, C. Note sur la bactériologie de la verruga du Pérou. Ann d'Inst Pasteur, 1908, XII, 591.

Letulle,<sup>10</sup> Escomel,<sup>11</sup> Giltner<sup>12</sup> and Izquierdo,<sup>13</sup> while just lately an organism closely related to the paratyphosus bacillus, type B, has been found by DeVecchi,<sup>9</sup> Barton,<sup>14</sup> Biffi<sup>15</sup> and others. Cell inclusion-bodies have also been reported.

#### DIAGNOSIS

In diagnosis one must always keep malaria in mind, for in fact the two diseases have been very frequently confused, and they are occasionally found together in the same patient. However, the therapeutic test must also be ruled out. In a patient having the cutaneous tumors as the predominant symptom it would also be necessary to think of neurofibromatosis (von Recklinghausen's disease). The affection occurring in a tropical country, framboesia and *Bouton d'Orient* would likewise have to be considered in a differential diagnosis. In the former, suitable examination for the specific spirochete would be sufficient, while in the latter there would be the history of painless ulcers on the exposed parts, in which proper examination would reveal the Leishmann-Donovan bodies.

#### PROGNOSIS AND TREATMENT

The prognosis of verruga should always be guarded, though the cases having the cutaneous tumors as their main symptom usually do better than the ones with the high fever.

The treatment is symptomatic and apparently of little avail. Quinin and the salicylates have been the drugs mostly relied on and it will be interesting to see what will be the effect of our new drugs, salvarsan and neosalvarsan. Perhaps they will be as effectual as in framboesia, and their use is to be recommended—at least as an experiment. Despite all treatment the cutaneous lesions usually last from four to six months, and even up to two years. In the Berne case the growths were practically all gone in a space of three months.

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9 DeVecchi, B. Ueber die Verruga peruviana. Arch f Schiff's u Tropenhyg, 1909, xiii, part 4, 143.

10 Letulle. Histological Study in Prof. Odriozola's monograph (Note 1).

11 Escomel, E. Anatomie pathologique du verrucome de Carrion. Ann d derm et d syph, 1902, iii, 961.

12 Giltner, H. A. Verruca Peruana or Carrion's Disease. Jour Am Med Assn, 1911, lvi, 2074, Abstr, Munchen med Wchnschr, 1912, No 8, p 440.

13 Izquierdo, V. Spaltpilze bei der Verruga peruviana. Virchow's Arch f path Anat, 1884, xcix, 411.

14 Barton. Quoted by DeVecchi (Note 9).

15 Biffi y Carbajal. Verruga peruviana und selweres Fieber Carrion. Arch f Schiff's u Tropenhyg, 1908, Part I. Quoted by DeVecchi (Note 9).

## EXPERIMENTAL TRANSMISSION

Outside of one experiment mentioned by Odrizola<sup>1</sup> on page 175 of his book, no attempt has ever been made to transmit the disease to lower animals. In this case a bitch was inoculated with the blood from a large verruga tumor. Later she had several growths on the paws and ears, delivered two dead pups and died. The experiment was rather indefinite, and no autopsy was done. In Jadassohn's case several of the tumors were excised, ground up into a "bier" and many cultures made on different media, though in vain. Like success also attended experiments with rabbits, guinea-pigs, doves, chickens, rats and a dog. But in working with apes the results were better. The first animal (*Cercopithecus sabaeus*) was inoculated on the eyebrows with some of the "bier," and in forty-five days several growths appeared which eventually reached the size of small cherries. One of these was excised for further transmission to a *Rhesus*, and in fourteen days tumor growths were noted which finally reached a larger size than in the first animal. Lesions from the second ape were successfully transmitted to still a third animal (a *Rhesus*), where the incubation period was only seven days. This ape died suddenly, autopsy revealing nothing, so that further inoculations had to be made with the almost healed tumors from Ape 2, and they were unsuccessful, though done intravenously. Rabbits, guinea-pigs, rats, white and gray mice, chickens and doves were also further experimented on, but in vain. In all these apes the blood-picture was at all times normal, and neither in them nor in the man was it possible to find in the blood or in the red cells of the tissue fluids any of the inclusion-bodies that have been reported by Bassett-Smith,<sup>7</sup> Galli-Valerio,<sup>16</sup> DeVecchi<sup>9</sup> and others, though practically all known parasite stains were used. Moreover, in none of the apes did the autopsy show changes that could in any way have been due to *Verruga peruviana*. The cutaneous lesions from both the man and the apes showed the same characteristic histological picture, which will be taken up more in detail in a later paper.<sup>17</sup> Here it will be enough to say that the growths showed a marked vascular proliferation along with the presence of many free red blood-cells in the tissues. Many mono- and polymorphonuclear leukocytes, plasma cells and fibroblasts were noted in the tissues and peculiar lymph-vessels inclusion-areas, thus far imperfectly noted and described, were also seen. By the use of no known tissue parasitic stain was it possible to find any of the acid fast bacilli, cell-inclusion parasites or other organisms that have been described by different men. Odrizola says he has made examinations in two types of patients. In the first class, where there is a cutaneous

16 Galli-Valerio B. Observations microscopiques sur la Verruga peruana ou maladie de Carrion. Centralbl f. Bakteriol, etc., 1911, lviin, Part 1 Orig. p. 228

17 A histological study will appear later in the *Journal of Cutaneous Diseases*

eruption and no temperature, he has always had negative results. In the second type, with eruption and temperature, he has always found a small bacillus. In such classes of patients Biffi, DeVecchi, Barton and others have also found an organism closely related to the paratyphosus bacillus, Type B, and it may be that the negative results are due in this case to the fact that the patient, at least to our knowledge, at no time had any temperature or other especial symptoms of the "*Fièvre grave de Carrion*." Is it possible that Carrion could have been inoculated from a *Verruga peruviana* patient suffering also from a different disease, Oroya fever or "*Fièvre grave de Carrion*," and that he succumbed to the latter before the "*Eruption de Carrion*" had an opportunity to make its appearance? This question and many others in regard to the advisability of separating the affection into two clinical and distinct entities can only be solved by future study with large amounts of material at hand. However, I feel safe in making at least the following conclusions:

#### CONCLUSIONS

1 In a case of *Verruga peruviana*, *Eruption de Carrion*, there was success in inoculating the disease into apes to the third generation, further transmissions being hindered only from want of material.

2 The lesions from the man and the apes resembled each other very closely histologically, were granulomatous in type and had peculiar lymph-vessel inclusion-areas.

3 None of the organisms mentioned as specific for the disease were found either in the lesions from the patient or from the animals.

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